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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

PEDIATRIC UROLOGY, SECOND EDITION ISBN: 978-1-4160-3204-5

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The Publisher

Library of Congress Cataloging-in-Publication Data
Pediatric urology / [edited by] John P. Gearhart, Richard C. Rink, Pierre D.E. Mouriqand. — 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4160-3204-5
1. Pediatric urology—Case studies. 2. Pediatric urology—Problems, exercises, etc. I. Gearhart, John P. II. Rink, Richard C. III. Mouriquand, Pierre D. E.
[DNLM: 1. Urologic Diseases. 2. Child. 3. Female Urogenital Diseases. 4. Male Urogenital Diseases. 5. Urogenital System. WS 320 P37533 2010]
RJ466.C54 2010
618.92'6--dc22
2009005819

Acquisitions Editor: Stefanie Jewell-Thomas
Developmental Editor: Colleen McGonigal
Publishing Services Manager: Frank Polizzano
Project Manager: Rachel Miller
Design Direction: Lou Forgione
Illustration Direction: Kari Wszolek

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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To my wonderful wife, Susan, and Baby Grace, who make coming home early my daily goal.
I will always be grateful to my teachers and role models, Roy Witherington, J. Herbert Johnston,
Patrick C. Walsh, and Robert Douglas Jeffs.

John P. Gearhart, MD

To my wife, Kanda, and my children, Andy and Stephanie, who have been a constant source of love and support, and to my brother Larry, who has shown the way. I am forever grateful for the encouragement and teachings of my mentors—Alan Retik, Hardy Hendren, and Mike Mitchell—and the support of my present and past partners, as well as my former residents and fellows. I dearly miss my first mentor, Dr. John Donohue, and my brother Skip, both of whom we lost this past year.

Richard C. Rink, MD

To my wife, Jessica, my children, David and Caroline, and stepchildren, Emma and Sophie:
Thank you for your patience and love.

To the memory of my father, Claude, who left us in November 2008:
He held my hand along beautiful paths.

To Philip Ransley, David Frank, and Maggie Godley, who are my essential companions.

To Captain and his indestructible joy of life.

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Chapter 36: Surgical Management of Female Genital Anomalies, Disorders of Sexual Development, Urogenital Sinus, and Cloacal Anomalies

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FOREWORD

The field of pediatric urology continues to change dramatically. Certainly there have been very significant advances since the first edition of this book was published in 2001. In this new edition, previous chapters have been updated and an impressive number of new chapters has been added. The new edition continues to be an international one edited by three well-known pediatric urologists from the United States and abroad.

The philosophy of the textbook is similar to that of the first edition—in other words, the editors and authors provide up-to-date information on the entire spectrum of pediatric urology, including new chapters devoted to magnetic resonance imaging of the pediatric urinary tract, tissue engineering, and neonatal emergencies. The second edition has been redesigned in a full-color format that is more readable. In addition, the content of the chapters has been updated with new topics, techniques, and procedures. The text and images will also be available online with the purchase of the book.

In summary, the second edition continues to be an excellent, updated, and comprehensive textbook edited by world-renowned pediatric urologists who have compiled a group of international experts to contribute to the textbook. This book should be of great benefit to all physicians caring for infants and children with pediatric urologic disorders.

Alan B. Retik, MD

PREFACE

Pediatric urology has matured a great deal over the last decade, and, with the onset of the third millennium, this new textbook is an important milestone not only for the third generation of pediatric urologists but also for all related specialists. This edition is more than a comprehensive update; in it, the leading specialists from around the world have shed new light on the various aspects of pediatric urology.

With the growing importance of new imaging, molecular biology, genetics, experimental surgery, minimally invasive surgery, antenatal uronephrology, and evidence-based medicine in the field, different and more pertinent approaches to many familiar but also less common situations are detailed here with a constant wish for clarity and honesty.

Such an enormous amount of data would not exist without the outstanding work done by three generations of pediatric urologists from all over the world, who have built our beautiful specialty brick by brick, article after article, textbook after textbook. They should all be thanked warmly. It is impossible to mention all of them here, but we could not preface this textbook without a special tribute to six of the "fathers" of modern pediatric urology: Sir David Innes Williams from Great Ormond Street Hospital, the late Mr. J. Herbert Johnston from Alder Hey Hospital, Kelm Hjalmas, John W. Duckett, Jean Cendron, and Robert D. Jeffs.

The three editors would like to give their deep thanks for the outstanding work done by all of the contributors in the production of this innovative textbook. They also wish to express their gratitude to Mr. Scott Scheidt from Elsevier who has been behind each step of the new edition with incredible efficiency, from its revision and update to its delivery.

Finally, the editors would not have spent their evenings and weekends for this textbook without the wonderful and permanent support of their families.

John P. Gearhart
Richard C. Rink
Pierre D. E. Mouriquand

PART I

BASICS

SECTION 1

EMBRYOLOGY AND PHYSIOLOGY OF THE URINARY TRACT

CHAPTER 1

EMBRYOLOGY OF THE UROGENITAL TRACT

Peter M. Cuckow

Human gestation starts with fertilization, defined by fusion of the nuclear material of a spermatozoon and a definitive oocyte, and continues until the birth of a fully developed infant approximately 38 weeks later. During the first 10 weeks, the body form and organ systems that are present at birth develop (embryogenesis). The remaining 28 weeks are spent in the maturation, growth, and development of function of the body, enabling independent life after separation from the placental support system. An understanding of embryogenesis and its disorders explains many of the anomalies encountered in pediatric urologic practice and offers some clues to the appropriate clinical approach to these conditions.

DEVELOPMENT OF EARLY URINARY TRACT PRECURSORS

After fertilization, the developing zygote, with its full diploid complement of genetic material, travels down the fallopian tube to reach the uterus. During the 5 to 6 days it takes to complete this journey, the zygote divides to form a ball of cells called a blastocyst. Further rapid divisions and the formation of two cavities on either side of an embryonic disc follow implantation of the zygote into the endometrium (Fig. 1-1). These cavities are called the amniotic cavity and the yolk sac. The disc itself is initially formed from two layers of cells—the ectoderm on its amniotic surface and the endoderm on its yolk sac surface. At approximately 15 days, the inpouring of cells from a differentiated midline area, called the primitive streak, forms a third layer of mesoderm throughout most of the disc. This is further subdivided into three parallel areas, designated laterally from the primitive streak as the paraxial, the intermediate, and the lateral plate mesoderm. It is largely from the intermediate mesoderm that the urinary and genital organ systems will develop.

In two areas of the early embryonic disc, the endoderm and ectoderm remain opposed. These form the buccopharyngeal membrane at the head end and the cloacal membrane at the tail end (see Fig. 1-1). As the embryo continues to grow

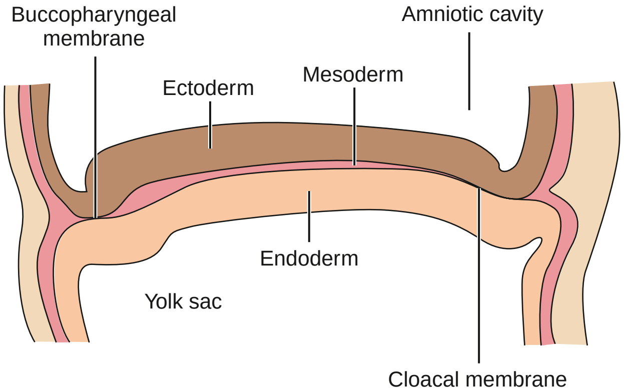

Figure 1-1 An early cross section of the human embryonic disc. The disc separates the ectoderm-lined amniotic cavity from the endoderm-lined yolk sac. Ingrowth of cells from the primitive streak forms a third layer between them, the mesoderm. This is deficient at the head and tail ends, the locations, respectively, of the buccopharyngeal membrane and the cloacal membrane.

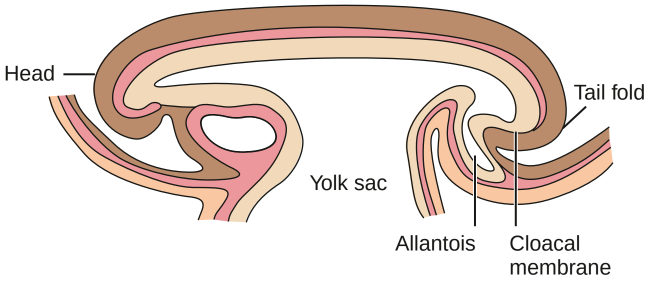

Figure 1-2 The embryonic disc has folded, including an endoderm layer from the yolk sac that will form the hindgut and foregut. The cloacal membrane faces anteriorly, and the cloaca is defined distal to the confluence of the hindgut and allantois.

rapidly, its dorsal surface bulges into the amniotic cavity, and its head and tail ends fold forward to form the head and the tail folds, respectively. During this process, the lining or endoderm of the yolk sac is included within the two folds, where it is the precursor of the foregut and the hindgut, respectively (Fig. 1-2). As folding of the tail end continues, the connecting stalk and allantois are formed and displaced onto the front surface of the embryo (see Fig. 1-2). The cloacal membrane is also brought to the front of the tail fold, below the allantois. The allantois gains continuity with the developing hindgut and defines the cloaca as the portion of hindgut distal to their confluence (Fig. 1-3). The cloacal membrane is seen on the surface of the embryo at the center of a depression called the proctodeum. On either side of this are two surface elevations, the urogenital folds, which join at their upper ends in the genital tubercle. Growth of the anterior abdominal wall above the cloacal membrane, coupled with regression of the tail fold, causes its relative displacement toward the tail end of the embryo, facing downward (Figs. 1-4 and 1-5).

A priority of the embryo is to establish the seeds of its own reproduction. Thus, early in its development, primordial germ cells are set aside in the wall of the yolk sac. These cells have ameboid characteristics that enable them to migrate later in gestation to take part in gonadal differentiation and the formation of the genital tracts.

RENAL DEVELOPMENT

From early in the 4th week of gestation, three nephric structures develop in succession from the intermediate mesoderm that runs the length of the embryo. The first, or pronephros, appears in the cervical portion and rapidly regresses, without forming any nephronlike structures (although it does develop excretory function in amphibian larvae and some fish). Subsequently, the appearance of tubular structures in the midportion (thoracic and lumbar sections) of the intermediate mesoderm heralds the development of the mesonephros.

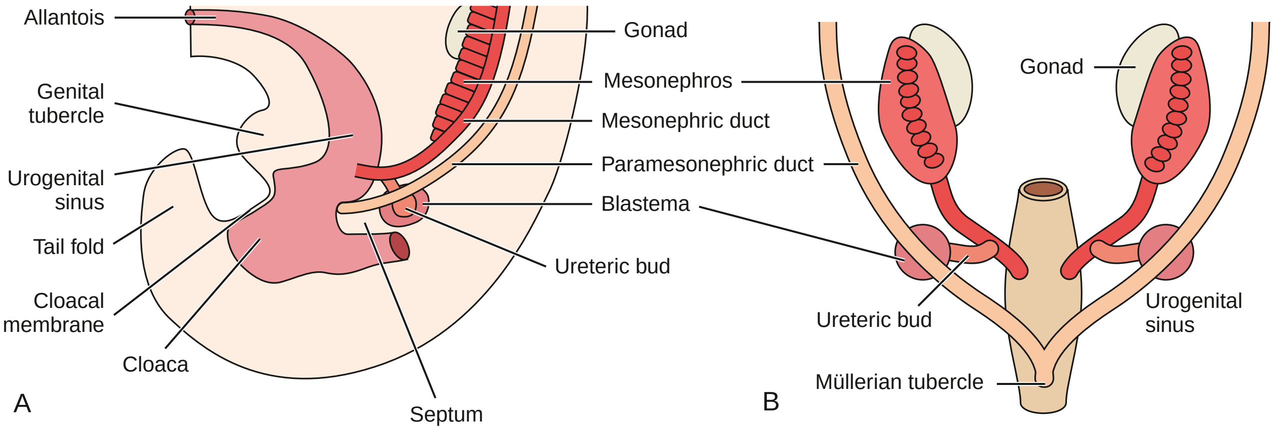

Figure 1-3 **A,** The tail end of the human embryo during the 5th week of gestation (lateral view). The ureteric bud begins to grow posteriorly from the distal part of the mesonephric duct. The urorectal septum advances forward to divide the cloaca into an anterior urogenital sinus and a posterior rectum. As it does so, infolding of the lateral walls of the cloaca helps to complete the division. The gonad precursors are visible anteromedial to the mesonephroi; their paired ducts descend lateral to the mesonephric ducts and join at the urogenital sinus to form the müllerian tubercle. The cloacal membrane faces forward and upward. **B,** The same gestation looking from behind the urogenital sinus. The mesonephric ducts enter the sinus posteriorly. The müllerian ducts come together and indent the sinus at the müllerian tubercle.

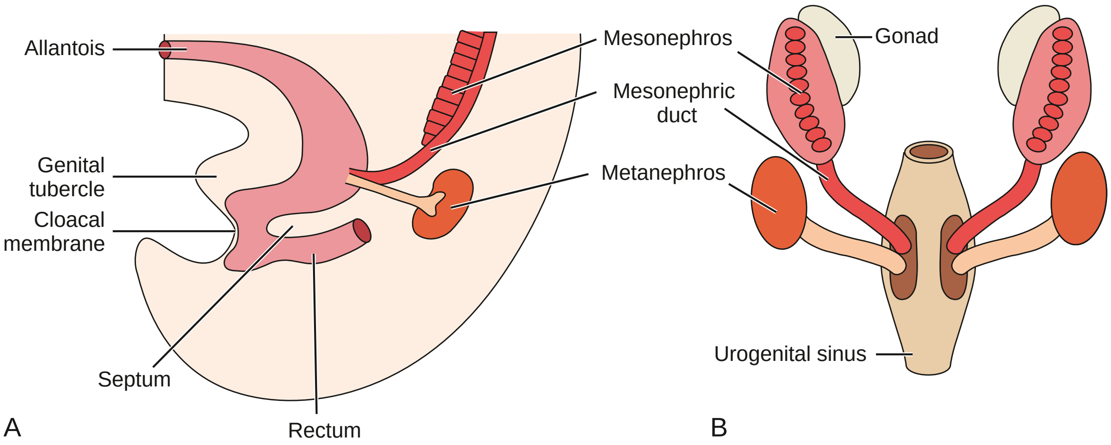

Figure 1-4 **A,** The tail end of the embryo during the 6th week of gestation (lateral view, müllerian and genital development not shown). The urorectal septum advances toward the cloacal membrane. The kidneys are forming, and the origin of the ureteric bud approaches the urogenital sinus as the end of the mesonephric duct is incorporated into its posterior wall. Growth of the anterior abdominal wall is accompanied by expansion of the vesicourethral canal. The orientation of the cloacal membrane is beginning to change. **B,** Same gestation, posterior view.

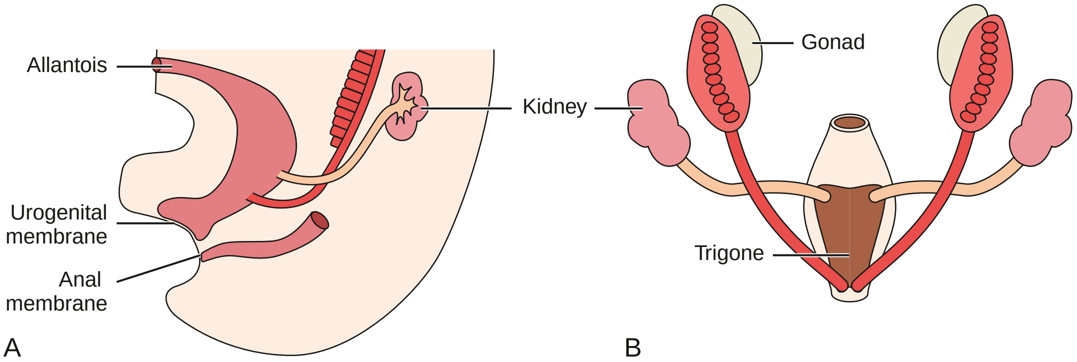

Figure 1-5 **A,** The tail end of the embryo during the 8th week of gestation (lateral view, müllerian and genital development not shown). The kidney ascends from the pelvis as the mesonephric duct, and its ureteric origins are further incorporated into the urogenital sinus. Cloacal septation is complete, and the membranes, which have started to degenerate, are facing downward. **B,** Same gestation, from behind the urogenital sinus. The trigone is formed with separation of the mesonephric ducts and ureteric orifices.

Mesonephric or wolffian ducts form lateral to this region and grow downward to enter the lateral wall of the cloaca. These primitive renal units possess capillary tufts at the proximal ends of simple nephrons and probably begin functioning at between 6 and 10 weeks, producing small amounts of urine (see Fig. 1-4). The mesonephros forms the definitive kidney in amphibians and most fish. At approximately 10 weeks of human gestation, the lower parts of the mesonephroi degenerate, leaving the upper nephrons, which will contribute to the developing genital duct system.

At the beginning of the 5th week of gestation, a diverticulum appears on the posteromedial aspect of the lower portion of the mesonephric ducts (see Fig. 1-4). This structure, the ureteric bud, grows backward toward the lowest or sacral portion of the intermediate mesoderm (called the metanephric blastema) and penetrates it late in the 5th week. The ureteric bud and metanephric blastema interact to induce nephrogenesis that continues throughout gestation and is complete just before term at 36 weeks. The tip of the ureteric bud dilates to form the renal pelvis, and then it begins to branch dichotomously. The first four generations coalesce to form the major calyces, and the sixth to eighth generations similarly fuse to form the minor calyces. The next eight generations form the definitive collecting duct system. Blastema cells collect around the tip of each collecting duct and form nephrons, comprising a Bowman capsule, proximal convoluted tubule, loop of Henle, and distal convoluted tubule. Branches of the internal iliac artery feed each nephron and form capillary tufts within the Bowman capsule. The branching of the ureteric bud is complete by about 14 weeks, but new generations of nephrons continue to be produced within the parenchyma throughout the remainder of gestation.

The embryonic kidney has a lobulated external appearance and ascends from its pelvic position during the 6th to 9th weeks. During this process, lower branches of the vascular supply degenerate as upper branches form successively from the aorta, until it attains its definitive renal artery and lies in its final lumbar position. The pelvic kidney faces anteriorly and will rotate medially about 90 degrees during its ascent so that the hilum faces anteromedially in the renal fossa.

Fetal urine is produced from the 10th week onward, but initially the plasma filtrate is little modified, because tubular function starts to develop only from the 14th week. Throughout the latter part of gestation, the fetal kidneys provide more than 90% of the amniotic fluid. An adequate volume of this fluid allows the fetus to move freely within the amniotic cavity and is important for its lung and skeletal development.

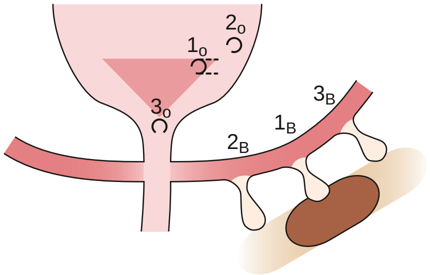

Figure 1-6 Development of the kidney and the final position of the ureteric orifice in the bladder related to the starting position of the ureteric bud on the mesonephric duct. A normally placed ureteric bud (1_B) induces normal renal development and results in a normally positioned, nonrefluxing ureteric orifice (1_O). A low origin (2_B) may induce an abnormal kidney whose orifice (2_O) is placed in a laterally ectopic position and is prone to reflux due to a short ureteric tunnel. A high origin (3_B) may also induce an abnormal kidney with an orifice that retains a closer association with the mesonephric duct (3_O). (After Mackie CG, Stephens FD, eds. Duplex kidneys: a correlation of renal dysplasia with the position of the ureteric orifice. *J Urol.* 1975;114:274.)

Anomalies of Ureteric Bud Development

Renal Agenesis and Dysplasia

Failure of development of the ureteric bud on one side results in renal agenesis, which is found in approximately 0.1% of the population. Alternatively, misplacement of the ureteric bud on the mesonephric duct prevents it from contacting the blastema with potential to form a normal kidney (Fig. 1-6). Instead, the bud misses and induces abnormal nephrogenesis, resulting in a dysplastic kidney. Buds arising below the normal position arrive at the urogenital sinus earlier in gestation and migrate further laterally, presenting a lateral ectopic orifice which is more prone to reflux owing to a shorter course through the bladder wall. This theory explains the association of reflux and renal dysplasia (Fig. 1-7). A bud arising higher on the mesonephric duct arrives at the urogenital sinus later in gestation and has less time to migrate away from the mesonephric duct opening. Such a ureter may drain in a medially ectopic position on the trigone or into one of the mesonephric duct derivatives. The kidneys that drained by these ectopic ureters are usually dysplastic.

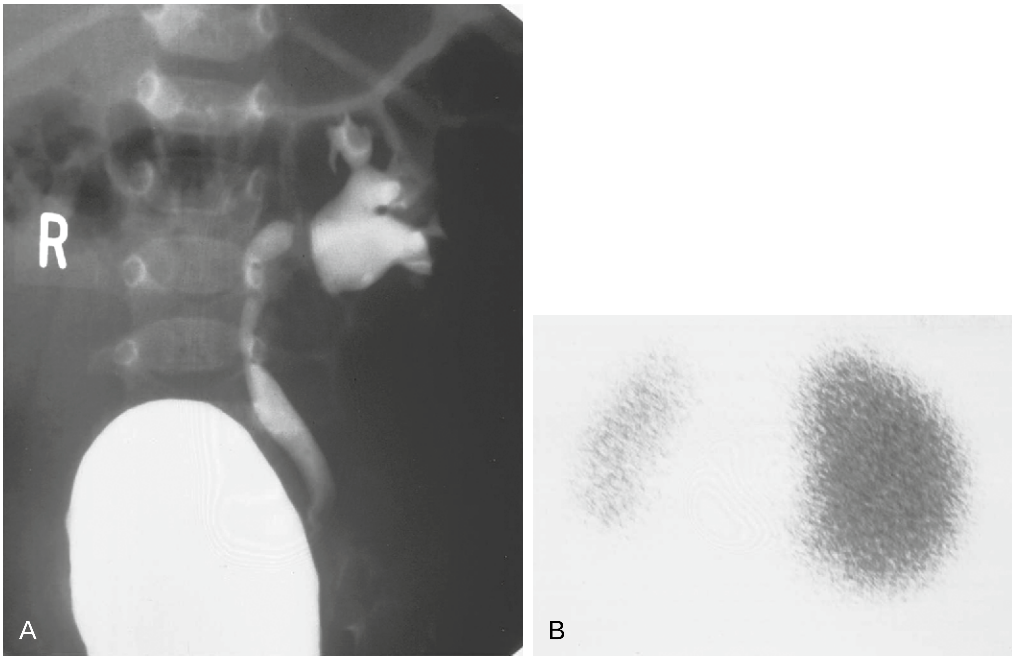

Figure 1-7 Cystogram **(A)** and technetium 99m dimercaptosuccinic acid (Tc^{99}-DMSA) scan **(B)** characterizing unilateral reflux in a boy. This condition manifested antenatally, and there was no history of urinary tract infection. The refluxing kidney is small and functions poorly, which is typical of the dysplasia that accompanies reflux.

Duplex Kidney

Duplex kidney, the most common of renal anomalies, arises when two ureteric buds occur on one side and induce upper and lower renal moieties. If a single bud divides close to its origin, the result is an incomplete duplex kidney with a common distal ureter (Fig. 1-8). If two separate buds form, the kidney is drained by two separate ureters. As it reaches the urogenital sinus, the lower ureter migrates laterally and crosses the upper ureter (the Weigert-Meyer law) (see Fig. 1-8). The lower moiety of the kidney is therefore more prone to reflux. The upper ureter, because it arrives at the urogenital sinus later, retains a closer association with the mesonephric duct opening and is prone to ectopia. The mechanism of ureterocele formation is unclear, but it may result from failure of involution of the Chwalla membrane (Fig. 1-9).

Anomalies of Renal Fusion, Position, and Rotation

Ectopic Kidneys

Kidneys that fail to ascend from the pelvis may also fail to rotate and have an anomalous blood supply derived from the aorta or pelvic vessels. A common example of this is the pelvic kidney (Fig. 1-10).

Fused Kidneys

If the two kidneys come together during their development in the pelvis, they may fuse. Most commonly, this results in a horseshoe kidney, in which fusion usually takes place between the lower poles (Fig. 1-11). Occurring in 1 in 500 members of the population, this anomaly is usually asymptomatic and is characterized by malrotated calyces seen at urography.

BLADDER, TRIGONE, AND LOWER URETERIC DEVELOPMENT

At about the same time that the ureteric buds appear (28 days), the partitioning of the cloaca commences. An ingrowth of mesoderm from the point of confluence of allantois and hindgut forms an advancing septum, which progresses toward the cloacal membrane (see Fig. 1-3). This, aided by the ingrowth of lateral or Rathke folds on either side, divides the cloaca into an anterior primitive urogenital sinus, which receives the mesonephric ducts, and a posterior rectum (see Fig. 1-4). This division is complete when the advancing edge of the urorectal septum reaches the cloacal membrane during the 6th week, dividing it into an anterior urogenital and a posterior anal membrane. The urogenital membrane breaks down during the 7th week, establishing continuity between the developing urinary tract and the amniotic cavity.

The upper part of the primitive urogenital sinus between the allantois and the mesonephric ducts is called the vesicourethral canal; it will form the definitive bladder. Growth of the anterior abdominal wall between the allantois and the urogenital membrane is accompanied by an increase in size and capacity of this bladder precursor. The allantois remains attached to the apex of the fetal bladder and extends into the umbilical root; it loses its patency and persists as the median umbilical ligament, otherwise known as the urachal remnant. By the 13th week, the interlacing circular and longitudinal strands of the smooth muscle of the trigone are discernible. By 16 weeks, these are refined into discrete inner and outer longitudinal layers and a middle circular layer; at this time, continence may be possible. The definitive urothelium is visible by 21 weeks' gestation.

During the process of cloacal septation, the mesonephric ducts distal to the ureteric bud origins (otherwise known as

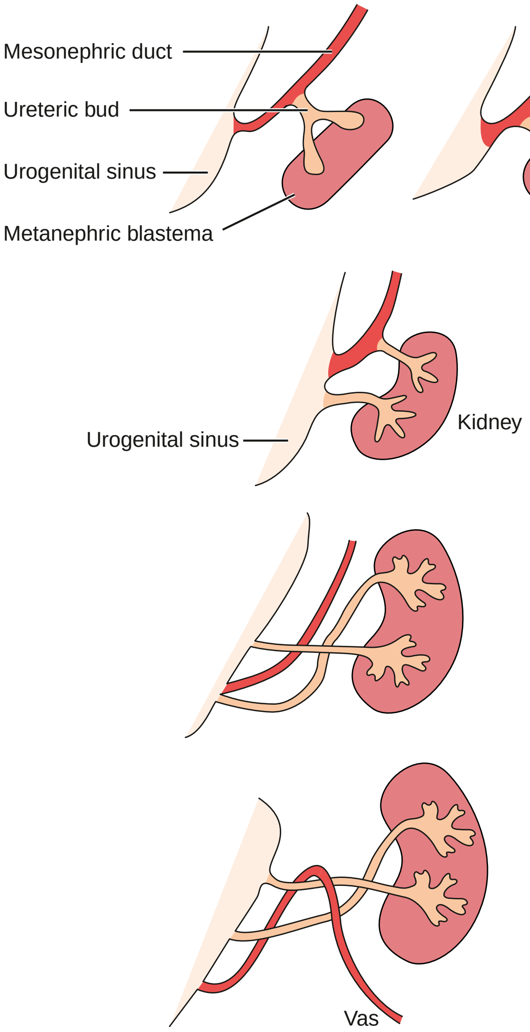

Figure 1-8 The embryogenesis of ureteric duplication. Partial duplication occurs when the ureteric bud divides after its origin to form two collecting systems with ureters that join above the bladder to terminate in a single orifice *(top left)*. If two separate buds arise, complete duplication is the result *(top right)*. As the bottom three images illustrate, the two ureteric origins are incorporated into the urogenital sinus at different times, so that they cross, causing the lower pole ureter to lie above and lateral to the upper pole ureter (the Weigert-Meyer law).

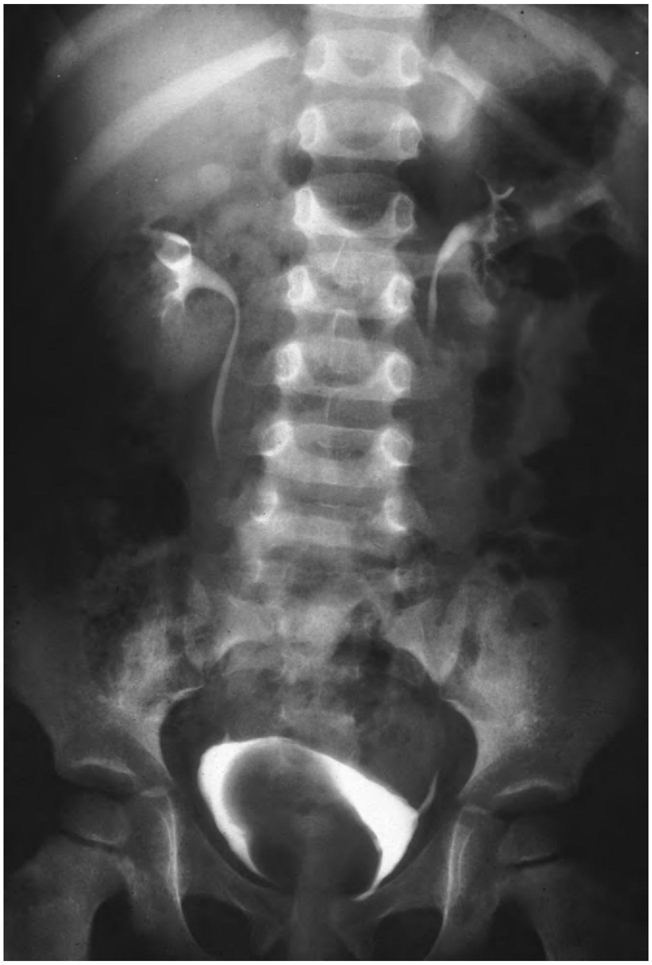

Figure 1-9 Intravenous urogram showing a right duplex system in a girl. The ureter from the poorly functioning upper pole drains ectopically into a ureterocele that is seen as a filling defect in the bladder.

the common excretory ducts) widen and become incorporated into the posterior aspect of the primitive urogenital sinus (see Fig. 1-4). As this continues, the posterior wall of the canal widens. The ureteric orifices arrive on the surface of this posterior wall early and become separated from the mesonephric duct orifices. As further incorporation of the lower mesonephric ducts occurs, the ureteric orifices move superolaterally relative to the mesonephric duct orifices (see Fig. 1-5). These stay close to the midline and descend into the developing posterior urethra. The epithelia of both ducts fuse in the midline, and the triangular area between them and the ureteric orifices defines the trigone (see Fig. 1-5).

During the ascent of the kidneys from the pelvis, the ureters rapidly elongate. Initially, their lumen is not apparent, but it develops cranially and caudally from the midpoint until early in the 8th week, when only a membrane persists between the lower ureter and the urogenital canal. By the middle of the 8th week, this Chwalla membrane disappears. The muscularization of the ureter is probably induced by drainage of the first secreted urine at about the 9th week of development. At 18 weeks of gestation, intrinsic narrowings can be discerned at the ureteropelvic junction and the ureterovesical junction.

The distal part of the primitive urogenital sinus will form the definitive urogenital sinus. In females, this gives rise to the entire urethra and the vestibule of the vagina. In males, it gives rise to the posterior urethra, and the anterior urethra is formed from the closure of the urethral folds.

Anomalies of the Urogenital Membrane and Cloacal Partitioning

Exstrophy

The exact embryologic origin of bladder exstrophy is unclear, but it is thought to be failure of growth of the lower abdominal wall, between the allantois and the urogenital membrane, coupled with breakdown of the urogenital membrane. This leaves a small, open bladder plate, a low-placed umbilical root, and diastasis of the pubic bones. The genital tubercle is probably placed lower in these patients so the cloacal membrane ruptures above it, leading to a penis with an open dorsal surface that is continuous with the bladder plate.

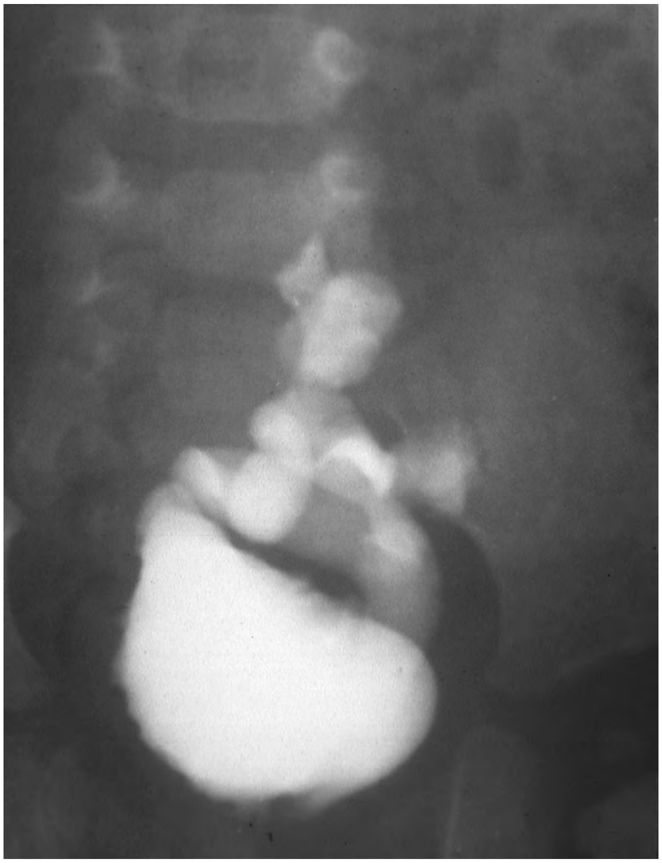

Figure 1-10 Cystogram demonstrating a pelvic kidney with a ureter that refluxes. Note the malrotated appearance of the calyces.

Cloacal Exstrophy

If the septum and Rathke folds also fail to partition the cloaca, the bladder plate is separated into two halves by a central hindgut plate. In this most severe variant of exstrophy, the phallus is often divided in two halves that may be widely separated.

Cloacal Anomalies

Incomplete septation of the cloaca leads to continued communication between the rectum and the urogenital sinus. The urethra, vagina, and rectum join into a common distal channel. The perineum is characterized by an imperforate anus and a single anterior opening.

Anomalies of the Trigone

Renal Agenesis

If the ureteric bud fails to develop on one side, the ipsilateral trigone also fails to develop, giving a characteristic endoscopic appearance. This is not usually associated with any continence problems.

Bilateral Single Ectopic Ureters

If both ureters maintain their relationship with the mesonephric duct, there is little separation between them, and the trigone fails to develop. Patients who have this anomaly have incompetent bladder outlets and poor capacity. Even after reconstructive surgery, the prognosis for urethral continence is very poor (Fig.1-12).

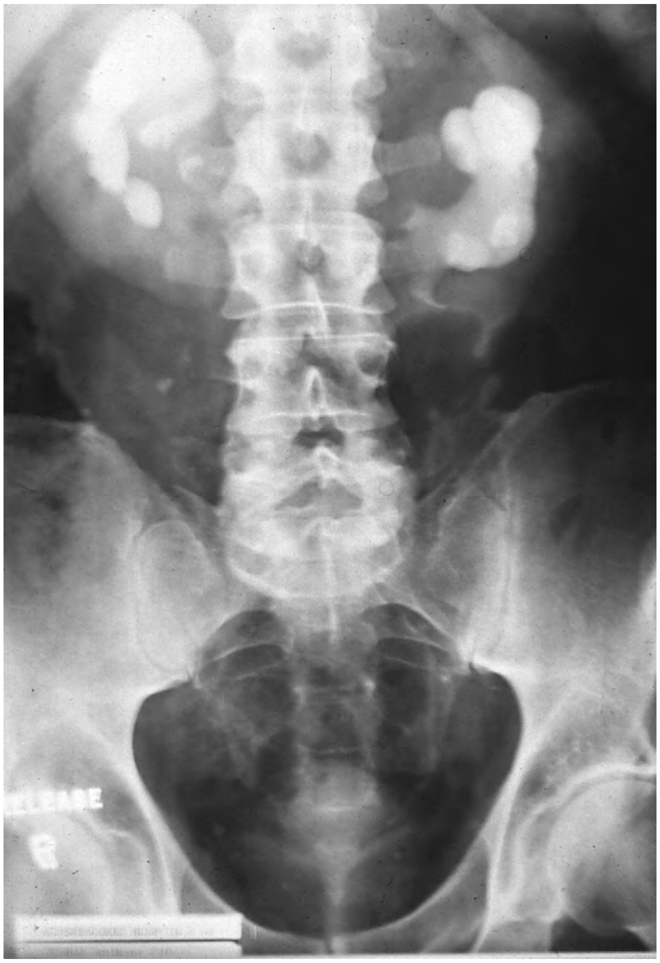

Figure 1-11 Intravenous urogram of a horseshoe kidney. The collecting system is malrotated, and the calyces face forward, giving a classic appearance. The lower poles are joined across the midline.

DEVELOPMENT OF THE INTERNAL GENITALIA

The gender of the individual has already been decided at fertilization, but during early genital development there is little discernible difference between the male and the female embryo. As stated previously, the germ cells arise from the yolk sac and migrate to the intermediate mesoderm. Here, they contribute to the genital ridges, which arise during the 5th week of gestation, anteromedial to the mesonephros (see Fig. 1-3). Interaction between the germ cells and the surrounding tissue creates primitive sex cords within the developing gonad, which is divided into an outer cortical layer and an inner medulla. At the same time, paramesonephric or müllerian ducts appear lateral to the mesonephric ducts and parallel to them in their upper course. As they approach the primitive urogenital sinus, these ducts converge and fuse in the midline, forming an elevation in its posterior wall called the müllerian tubercle (see Fig. 1-3).

From the 6th week, these early structures develop divergently in a male or a female direction. Ovaries arise principally

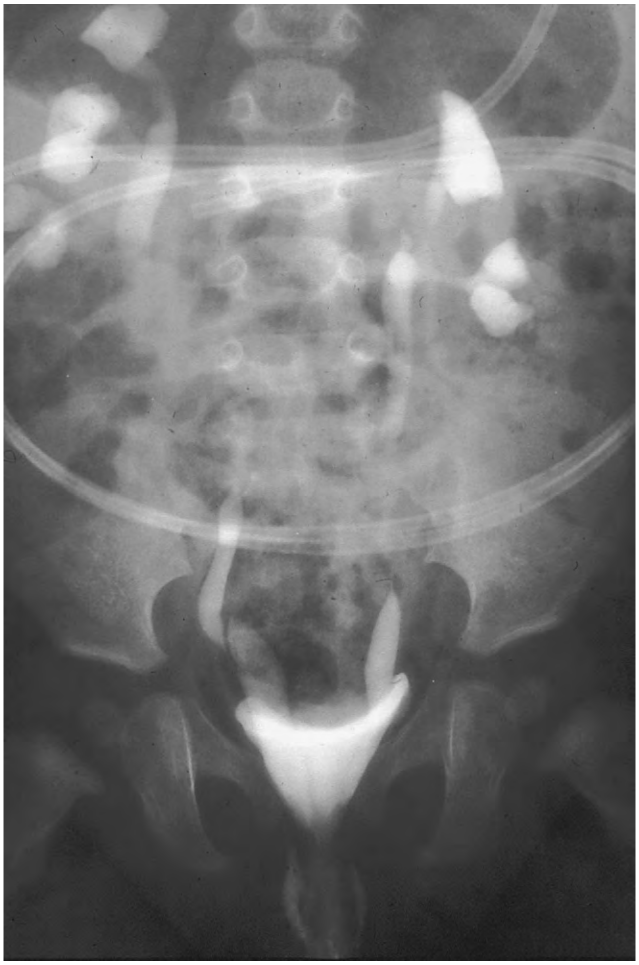

Figure 1-12 Intravenous urogram demonstrating bilateral single ectopic ureters. These drain into the urethra below an incompetent and abnormal-looking bladder neck. Although they appear to function well in this case, the kidneys in individuals with this rare anomaly may be dysplastic.

from the cortex of the indifferent gonad and their duct system from the paramesonephric (müllerian) duct, whereas the mesonephric (wolffian) duct degenerates. In contrast, the testis develops from the medulla of the indifferent gonad and its ducts from the mesonephric duct, whereas the paramesonephric duct degenerates (Fig. 1-13).

Female Development

Female development is the default pathway for genital development that is followed in the absence of the *SRY* gene product or testis-determining factor. The primitive sex cords degenerate, and secondary sex cords grow out from the cortex of the gonad into the surrounding tissue. The germ cells are incorporated into these, and primary oocytes form. These undergo meiotic division and then become quiescent until puberty. The paramesonephric ducts develop open, funnel-shaped, proximal ends that will become the fimbriated open ends of the uterine tubes. Distally, their merged portion enlarges to form the fundus and body of the uterus. At the müllerian tubercle, there is first a downgrowth of solid tissue within the urorectal septum, toward the fetal perineum, called the vaginal plate. This develops a lumen by the 20th week of gestation. The upper two thirds of the vagina are thought to arise from the paramesonephric system, whereas the lower third derives from the urogenital sinus itself. The vaginal lumen remains separated from the vestibule by the hymen.

The mesonephric ducts regress, leaving vestigial remnants at their proximal and distal ends. These are the epoöphoron and the paroöphoron in the mesentery of the ovary and the Gartner cyst in the wall of the vagina. A mesodermal band, the gubernaculum, extends from the lower pole of the ovary toward the inguinal region, crossing the inguinal canal and terminating in the labium majorum. As the ovary descends into the pelvis, the gubernaculum is folded within the broad ligament of the uterus and attaches in its midpoint to the junction of the uterine body and tube. Proximal to this attachment, it becomes the ovarian ligament, and distally it is the round ligament of the uterus.

Male Development

Male development is initiated by testis-determining factor, which is encoded on the short arm of the Y chromosome. The medulla of the indifferent gonad responds to the presence of this factor by growth of the primitive sex cords within the medulla and differentiation into the seminiferous tubules and the rete testis. The seminiferous tubules contain primordial sperm cells or spermatogonia that, unlike in the female gonad, remain quiescent until puberty. Developing Sertoli cells within the embryonic testis produce müllerian inhibiting substance during the 7th week of gestation. Müllerian inhibiting substance brings about male development by first causing regression of the müllerian system. It also stimulates Leydig cells to produce testosterone, under the influence of placental human chorionic gonadotropin, during the 8th week of gestation.

Testosterone acts on the mesonephric duct system to cause it to develop into the male genital ducts. Proximally, this results in the formation of the epididymis, which becomes connected to the rete testis via the residual mesonephric tubules (see earlier discussion). Distal to that point, the duct acquires a smooth muscle wall and becomes the vas deferens. At the lower end, just before the termination of the epididymis (the ejaculatory ducts), a diverticulum grows laterally to form the seminal vesicle. In the prostatic portion of the urethra, testosterone induces budding of the epithelium into the surrounding tissue, forming the ducts and stroma of the prostate gland, respectively, at around 10 weeks of gestation. The bulbourethral glands grow outward from the anterior urethra and develop in a similar manner.

Small portions of the regressed paramesonephric ducts persist as vestigial structures in the male. At their proximal ends, they form the appendix testis at the upper pole of the testis, and distally the prostatic utricle opens into the prostatic urethra and is equivalent to the proximal vagina. The upper end of the mesonephric duct persists as the appendix of the epididymis.

As the mesonephros regresses, the testis becomes detached from its anteromedial surface and floats free in the peritoneal cavity on a mesentery. As with the ovary, a mesodermal band or gubernaculum extends from the lower pole of the testis, passing down the posterior abdominal wall toward the inguinal region, where it traverses the abdominal wall musculature (the future inguinal canal). Because the length of this structure remains the same throughout embryonic and fetal growth, the testis is drawn down into the pelvis. In the 6th month of gestation, a pouch of peritoneum, the processus vaginalis, extends through the inguinal canal in front of the gubernaculum and into the scrotum. Testicular

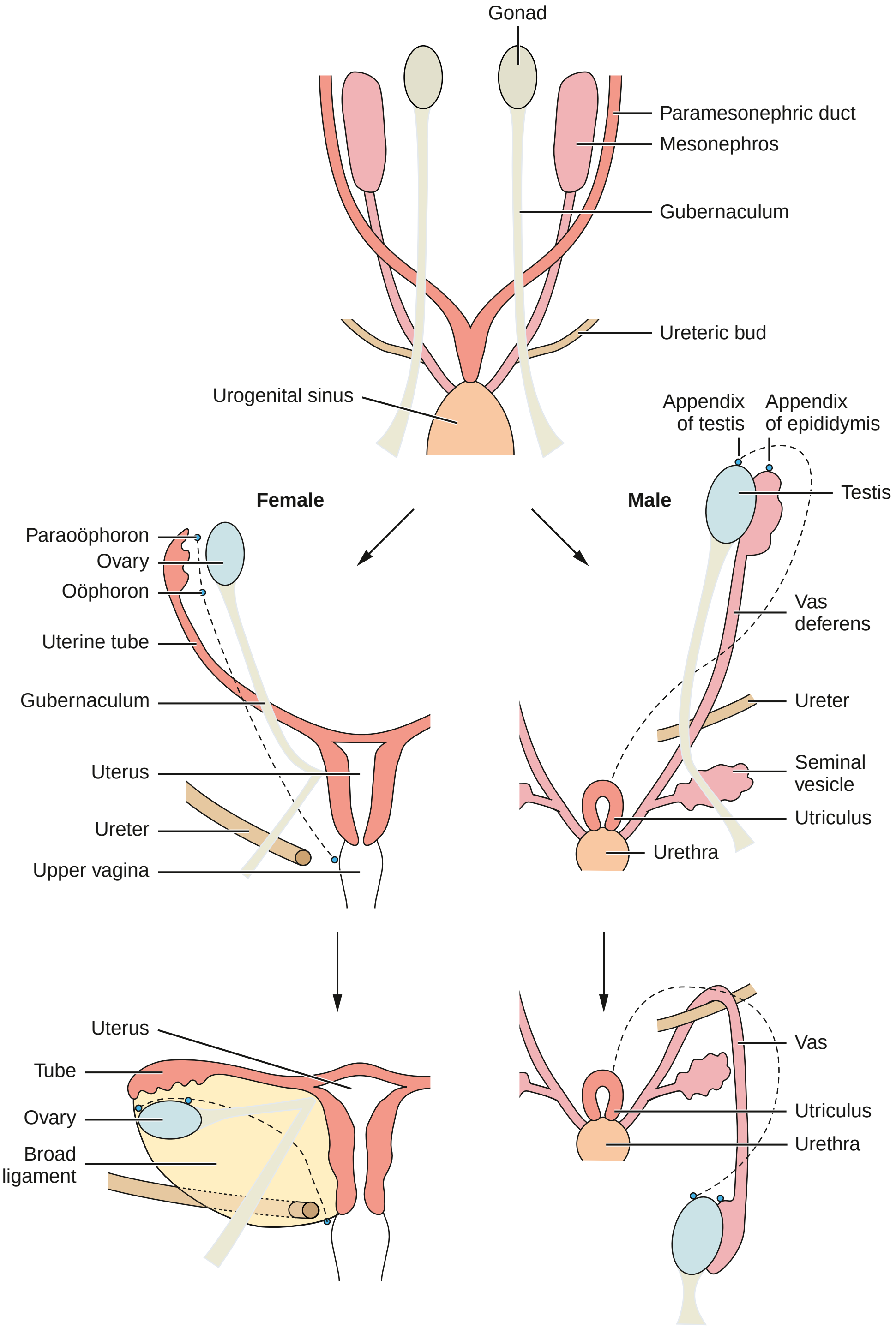
Gonad
Paramesonephric duct
Mesonephros
Gubernaculum
Ureteric bud
Urogenital sinus
Appendix of testis
Appendix of epididymis
Female
Male
Testis
Paraoöphoron
Ovary
Oöphoron
Uterine tube
Gubernaculum
Uterus
Ureter
Upper vagina
Vas deferens
Ureter
Seminal vesicle
Utriculus
Urethra
Uterus
Tube
Ovary
Broad ligament
Vas
Utriculus
Urethra

Figure 1-13 Internal genital development. After an indifferent phase, development follows a male or female pathway. In the female, the gonad differentiates into an ovary, and the paramesonephric ducts form the tubes, uterus, and upper vagina. The mesonephric duct degenerates and forms the ovarian and round ligaments, with vestigial remnants persisting as the epoöphoron, the paroöphoron, and Gartner cyst. In the male, the gonad differentiates into a testis and the mesonephric duct into the epididymis and vas deferens. The testis is united with its duct system through remnant tubules from the mesonephros, and the upper end of the mesonephric duct forms the vestigial appendix of the epididymis. The paramesonephric duct persists as the vestigial appendix testis and the prostatic utricle.

descent occurs on the posterior wall of this, so that the testis appears suspended within it, and is complete by the end of the 8th month. The proximal part of the processus is obliterated by birth, whereas the distal part persists around the testis as the tunica vaginalis (Fig. 1-14).

Anomalies of the Müllerian System

Incomplete fusion of the müllerian ducts in the female gives rise to a variety of uterine and vaginal anomalies. Depending on the level of the incomplete fusion, the uterus may be double, it may have a complete or partial septum, and the

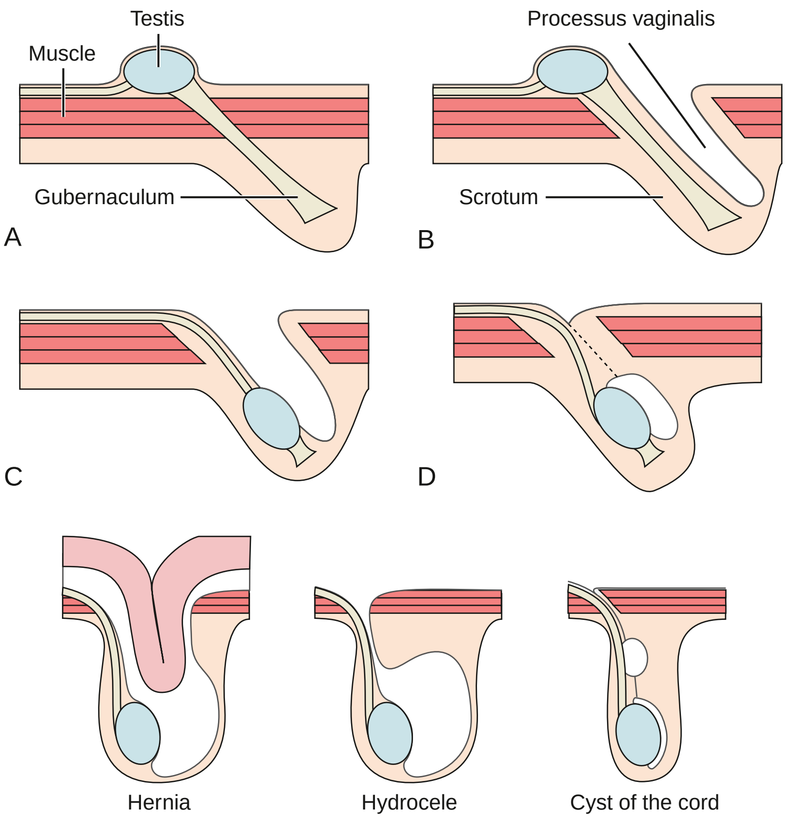

Figure 1-14 **A-D,** Development of the processus vaginalis and testicular descent. The gubernaculum traverses the abdominal wall musculature. The processus vaginalis extends along the gubernaculum, and the testis descends on its posterior wall, so that the body of the testis lies within it. The connection with the abdominal cavity is obliterated, leaving a peritoneum-lined space anterior to the testis, the tunica vaginalis. Failure of obliteration of the processus vaginalis results in a hernia or hydrocele, depending on the lumen of the connection. Occasionally, a cyst forms along the inguinal canal, representing a hydrocele of the cord.

vagina may be double or single. Occasionally, one of the uterine "horns" is rudimentary or missing.

Anomalies of the Processus Vaginalis

Failure of obliteration of the processus vaginalis leads to a spectrum of anomalies. If its lumen is sufficient, abdominal contents may be extruded into it and form a hernia. If the connection is too small to admit bowel, peritoneal fluid can collect in the tunica vaginalis and form a hydrocele. Occasionally, cystic remnants along the cord form localized swellings (see Fig. 1-14).

DEVELOPMENT OF THE EXTERNAL GENITALIA

As with the development of the internal genitalia, there is an early indifferent phase of the external genitalia, which persists to the 3rd month of gestation. Early development is characterized by the appearance of urogenital folds on either side of the cloacal membrane, which fuse anteriorly at the genital tubercle (Fig. 1-15). Lateral to these, larger swellings—the labioscrotal folds—become apparent and come together posteriorly between the urogenital and anal membranes as they separate. The urogenital membrane breaks down during the 7th week, opening the urogenital sinus to the amniotic cavity.

Female Development

In females, enlargement and subsequent folding of the genital tubercle forms the clitoris. The structures of the perineum do not fuse across the midline. The urogenital folds persist on either side of the introitus as the labia minora. The labioscrotal folds form the labia majora, which meet posteriorly at the fourchette. The urethra opens anterior to the vaginal opening, which is obscured by the hymen until late in gestation (see Fig. 1-15).

Male Development

Male external genital development depends on the conversion of testosterone to the more active dihydrotestosterone and its subsequent action via tissue receptors. The genital tubercle enlarges into the penis, and as it does, cells grow into its inferior surface to form the solid urethral plate. Subsequent involution results in a deep groove on the undersurface of the penis. The tip of the penis expands to form the glans. Unlike in females, male development continues by fusion of first the urogenital and then the labioscrotal folds across the midline. The penile urethra forms by fusion of the genital folds across the groove proximally. Distally, canalization occurs from the tip of the glans to complete the urethra and the expanded fossa navicularis. This process is complete by the end of the 20th week of gestation. The labioscrotal

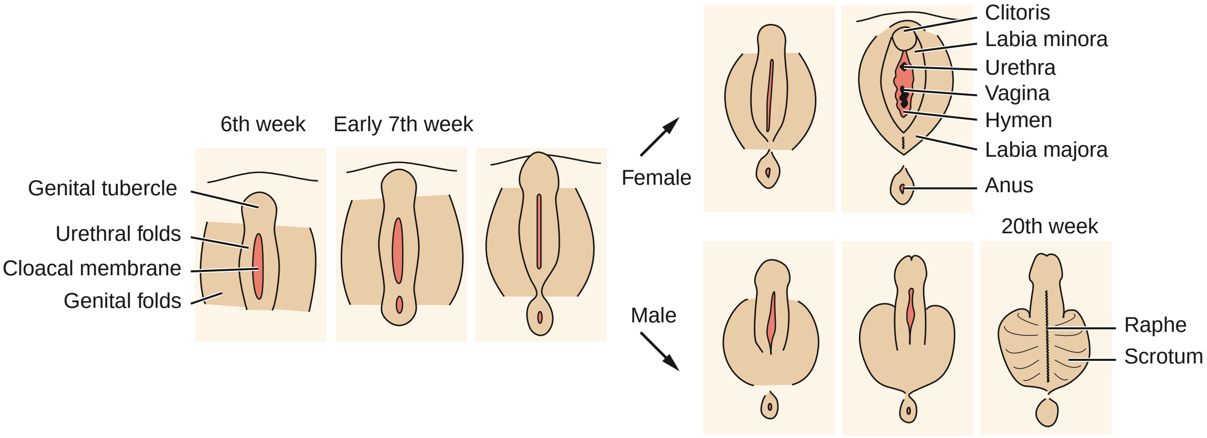

Figure 1-15 External genital development. After an indifferent phase, male and female paths diverge. In females, the genital tubercle enlarges and folds to form the clitoris. The genital folds form the minor labia, and the labioscrotal folds form the major labia. In males, the genital tubercle enlarges to form the penis. The genital folds fuse in the midline to form the penile urethra. The glanular urethra forms by invagination. The labioscrotal folds fuse across the midline to form the scrotum.

folds enlarge into the scrotum and fuse behind the penile urethra in a midline raphe. The foreskin arises from the base of the glans and grows more on the dorsal surface of the penis. As it advances distally, it also grows ventrally, covering the glans and meeting and fusing in a continuation of the midline raphe (see Fig. 1-15).

Abnormalities of the Genitalia

Hypospadias

The male anomaly of hypospadias is characterized by failure of development of the urethra to the tip of the penis. In the least severe form, the urethra opens distally and probably represents failure of glanular canalization. Failure of fusion of the genital folds results in a midshaft or proximal shaft opening. In the most severe type, complete failure of midline fusion results in an orifice between the halves of a cleft scrotum. In the more severe types, ventral curvature or chordee of the phallus is also seen.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is the most common of the intersex disorders, comprising about 80% of patients. Normal müllerian development takes place, but an enzyme defect in the steroid pathway leads to a deficiency in the end hormone product. This leads to hypertrophy of the adrenal glands as they try to redress the imbalance, resulting in large quantities of intermediate products with androgenic properties. These products stimulate the external genitalia of females, bringing about enlargement of the phallus, which may resemble a hypospadiac penis. The introitus is closed, and the urethra and vagina join in a single common channel before opening on the perineum. No gonads are palpable.

REFERENCES

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CHAPTER 2

NEPHROUROLOGY FROM FETUSHOOD TO ADULTHOOD

George Haycock

During the 20th century, much was learned about the nature of renal function in adult humans and animal models, and methods for measuring it are well established. By contrast, reliable information concerning renal function in infancy and early childhood has been available for only about 50 years, and for less than that in the premature infant. For obvious reasons, access to the human fetus for the purpose of physiologic studies is difficult, and therefore very little was known about fetal renal function until the last decade of the 20th century. The introduction of high-resolution ultrasound examination of the fetus during pregnancy has made it possible to identify urinary tract malformations quite early in gestation. Consequently, it has become desirable to identify tests capable of predicting renal functional outcome after birth in fetuses in whom a urinary tract anomaly has been detected. This has provided an incentive for more intensive physiologic study of both human and animal fetuses, and although much remains to be learned, it is now possible to summarize what is known about fetal renal function and to compare it with that observed in the infant after birth. This chapter focuses mainly on information available from investigations in human subjects, supplemented occasionally by the results of animal studies when data of human origin are lacking.

ELEMENTS OF RENAL FUNCTION

The main function of the kidney is *homeostasis*, originally defined by Claude Bernard as maintenance of the constancy of the internal environment. The internal environment is the extracellular fluid (ECF). Homeostasis is therefore the maintenance of the volume and composition of the ECF. The main threats to the stability of the ECF are the consequences of dietary intake and the production of metabolic waste substances by the body cells. The role of the kidney in this process is to detect small changes in the volume or composition of the ECF and to adjust the volume and composition of the urine so as to offset the tendency to change (negative feedback). For example, if water is ingested in excess of body need, the amount of solute-free water excreted by the kidney increases, resulting in a water diuresis and avoiding dilution of the body fluids. Similarly, changes in the amount of sodium taken in the diet, after adjustment for nonrenal losses, are matched by changes in the excretion rate of sodium in the urine.

Because sodium chloride (NaCl) is the principal determinant of ECF volume, the capacity to regulate salt excretion is of special importance to health and survival, and the capacity of the adult kidney to vary the urinary Na excretion rate is extraordinary. Some human populations survive and thrive on a daily salt intake as low as 10 mmol, whereas others may ingest as much as 1000 mmol/day. Bearing in mind that nonrenal Na losses are normally only 5 to 10 mmol/day, it is apparent that the healthy kidney can alter the urinary excretion rate of Na by almost three orders of magnitude and that, when necessary, it has the capacity to elaborate virtually Na-free urine. This ability is vital to survival when salt intake is low, as in a newborn human infant fed on human milk.

The mammalian kidney adjusts the volume and composition of the urine by the production of a very large volume of plasma ultrafiltrate (glomerular filtrate) and the reabsorption of more than 99% of that volume in most circumstances. A 70-kg human produces approximately 180 L of glomerular filtrate daily, of which each liter contains 140 mmol of Na; therefore, about 25,000 mmol of elemental Na, equivalent to almost 1.5 kg of salt, is removed from the ECF. If the daily dietary intake of salt is in the range of 5 to 10 g (85 to 170 mmol), as is typical of a Western diet, substantially less than 1% of the filtered Na can be excreted in the urine if urinary excretion is to equal dietary intake, which it must for homeostasis to be achieved. This means that more than 99% of the filtered Na is reabsorbed by the tubules; in other words, the *fractional sodium excretion* (FE_{Na}) is less than 1%. Tubular Na reabsorption is an active, energy-dependent process that accounts for most of the energy and oxygen consumption of the kidney; glomerular filtration, on the other hand, is energized by the force of myocardial contraction. The fractional excretion of filtered water is also usually less than 1%. In consequence, the urinary concentrations of filtered solutes that are not reabsorbed (e.g., creatinine) or are incompletely reabsorbed (e.g., urea) are elevated many times over their concentration in plasma.

FUNCTIONAL SEGMENTATION OF THE NEPHRON

The functional unit of the kidney is the nephron. A postmortem study of adults aged 16 to 87 years without evidence of renal disease found that each normal human kidney had between 330,000 and 1,050,000 nephrons (mean, 617 ± 154 × 10^6); therefore, each individual had between 660,000 and 2 million of them.[1] However, this and another study[2] showed a decline in glomerular number with age, so that the number in healthy young adults is probably greater than in older people. This was supported by a report investigating glomerular number in relation to blood pressure, which found that the median count in nonhypertensive white adults aged 35 to 59 years was 1,429,200 per kidney; however, only about half this number were found in hypertensive subjects matched for sex, age, height, and weight.[3]

Proceeding in a "downstream" direction, each nephron can be divided into functional segments or components (Fig. 2-1). The *glomerulus* is the ultrafilter that separates glomerular filtrate from plasma. The *proximal tubule* reabsorbs approximately two thirds of filtered salt and water and virtually all of the nutritionally important components of filtrate, such as glucose, amino acids, and bicarbonate. Reabsorption in the proximal tubule is isotonic, which means that the osmolar concentration of the fluid leaving the proximal tubule is the same as that entering it (i.e., the same as plasma). The *loop of Henle* is responsible for the reabsorption of about one quarter of the total filtered Na. Salt is reabsorbed without water in the ascending limb of the loop, so that the fluid leaving the

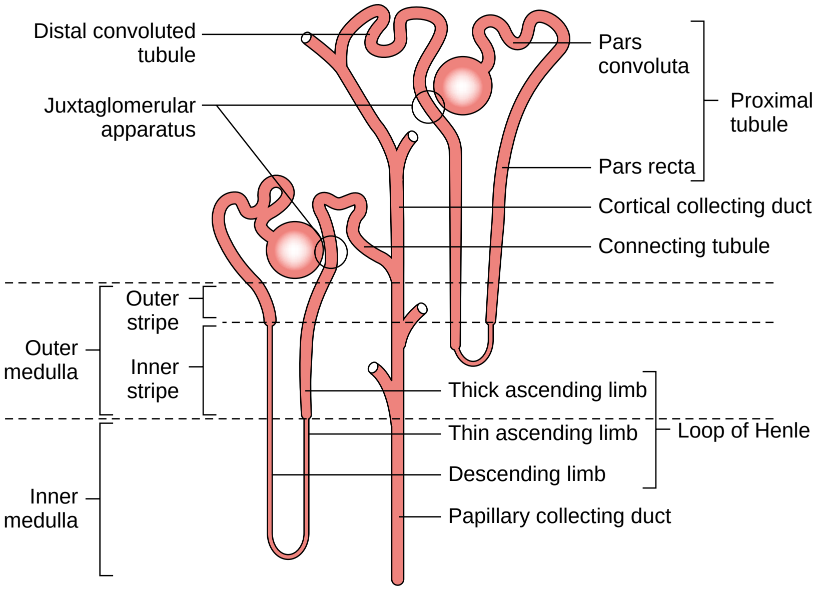

Figure 2-1 Schematic representation of the anatomy and orientation of nephrons in the human kidney. Two types of nephron are depicted: the superficial cortical nephrons, with short or absent loops of Henle (uppermost in the diagram), and the deep or juxtamedullary nephrons, with long loops of Henle. In the human, about 80% of the nephron population is of the superficial type, and 20% of the juxtamedullary type.

ascending limb is hypotonic to plasma at all times, regardless of whether concentrated or dilute urine is being produced. For this reason, the thick-walled part of the ascending limb of the loop, called the thick ascending limb (TAL), is also known as the *diluting segment* of the nephron.

The reabsorption of Na without water in the loop is the active step in the generation of the hypertonic medullary interstitium that is necessary for the production of urine more concentrated than plasma. The *distal convoluted tubule* and *collecting duct* are responsible for reabsorption of the final 10% or so of filtered Na and for active secretion of potassium and hydrogen ions. The *medullary collecting duct* is also responsible for the formation of concentrated urine by osmotic reabsorption of water under the influence of antidiuretic hormone. All of these functions are quantitatively less developed in infants than in adults, and still less so in premature infants and fetuses. However, there are good reasons for interpreting the low level of measured renal function in the infant born at or near term as appropriate to the needs of the individual at that stage of development, rather than being immature in the sense of placing the baby at a biologic disadvantage.

RENAL FUNCTION IN THE FETUS

Morphologic Background to the Development of Fetal Renal Function

The embryologic development of the kidney is described in Chapter 1, Embryology of the Urogenital Tract. Briefly, the kidney develops from the most caudal segment of the nephrogenic ridge, the *metanephros*, a specialized population of mesodermal cells that condenses around the tip of the ureteral bud from about 5 weeks' gestation. As the ureteric bud branches and rebranches, forming first the major calyces, then the minor calyces, and then the arborizing system of collecting ducts, nephron formation is induced in relation to the successive divisions of the duct system. Nephrogenesis proceeds centrifugally: nephrons that eventually lie most deeply in the cortex (the *juxtamedullary* nephrons) are the first to be formed, and those in the most superficial (*subcapsular*) portion of the cortex are formed last. The first few generations of nephrons atrophy without having functioned. The first permanent nephrons, and the production of urine, dates from 8 to 10 weeks' gestation; the last nephrons are formed by 36 weeks.[4] Although renal mass continues to increase rapidly after 36 weeks, this is due to enlargement of tubules, not the development of new nephrons. The timing of the major events in the intrauterine development of the human kidney is summarized in Figure 2-2.

Measurement of Renal Function in the Human Fetus

Direct studies of renal function are ethically impossible in normal human fetuses. However, a good deal of information has been obtained by noninvasive techniques, as well as by more direct methods in fetuses who were being investigated for suspected renal abnormalities in utero but were found after birth to have normal renal function. The latter group of subjects is a reasonable surrogate for strictly normal fetuses as regards information on blood and urine composition.

Glomerular Filtration Rate

The Fetal Medicine Group at King's College Hospital, London, has published data in three separate papers that can be combined to calculate mean GFR (creatinine clearance) in normal fetuses from 20 weeks' gestation to term. In the first of these reports,[5] blood samples were obtained from 344 singleton fetuses and biochemical analyses were performed, including plasma creatinine and electrolyte concentrations. In the second paper,[6] fetal urine flow rate (V) was estimated by extremely frequent ultrasonography of the fetal bladder in 85 healthy fetuses. Regression analysis of the slope of bladder filling against time was used to calculate V. The third study[7] measured urine biochemistry from fetuses with dilated urinary tracts; 27 of these fetuses survived with normal renal function or died of other causes but were found to have normal kidneys at postmortem examination. Although there is considerable scatter of values for all three variables (V and urine and plasma creatinine concentrations), mean values can be derived for each week of gestation, and, using these values, creatinine clearance (C_{Cr}) can be calculated from the following formula:

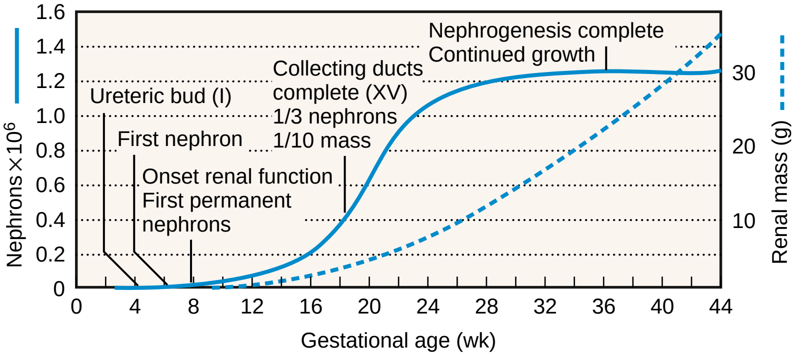

Figure 2-2 Schematic diagram depicting the major landmarks in the intrauterine development of the human kidney. The roman numerals indicate the number of generations of branching of the ureteric bud at the indicated time points.

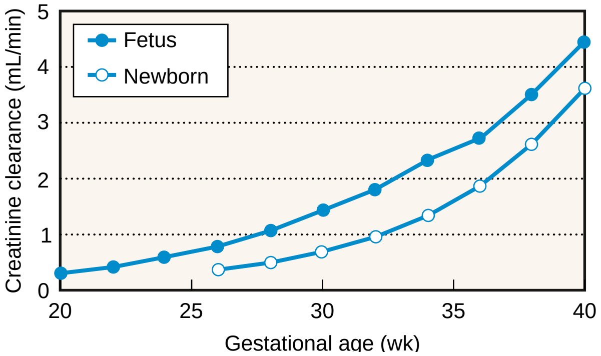

Figure 2-3 Creatinine clearance in fetuses (calculated as described in the text) and in newborn premature infants at comparable postconceptional ages. (Data from references 5 through 8.)

$$C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$$

where U is the urine concentration, P is the plasma concentration, and V is the urine flow rate. Results for fetuses from 20 weeks' gestation to term are shown in Figure 2-3 and are compared with those for newborn babies of the same absolute gestational age who were born at least 3 days before the study.[8] At all ages within the study period, creatinine clearance is substantially greater in the fetus than in the neonate. Although creatinine clearance has not been directly validated as a measure of glomerular filtration rate (GFR) in human fetuses, the agreement with clearance of sodium iothalamate, a well-documented marker for GFR, has been shown to be excellent in the sheep fetus.[9]

Renal Blood Flow and Filtration Fraction

Renal blood flow (RBF) has been estimated in human fetuses using color pulsed wave Doppler ultrasonography.[10] The method was previously validated by the same authors in studies of the fetal lamb,[11] in which estimates obtained by this technique agreed closely with those made using a perivascular flow probe placed directly around the renal artery. In the human fetuses, they obtained mean values for two kidneys of 40 mL/min at 22 weeks' gestation, 80 mL/min at 30 weeks, and 130 mL/min at 36 weeks. This amounted to 6.8%, 5.2%, and 5.2%, respectively, of the simultaneously determined cardiac output, figures that compare reasonably well with values of 4.9% and 3.2% obtained in immature and mature baboon fetuses, respectively. However, this estimate of human fetal RBF seems remarkably high, given that RBF measured directly by renal vein catheterization in two infants during the first 2 weeks of extrauterine life was in the range of 30 to 50 mL/min.[12] Furthermore, if these estimates for RBF are combined with those calculated for fetal GFR, the filtration fraction would be approximately 1% at 22 weeks, 1.8% at 30 weeks, and 2.3% at 36 weeks, very low compared with all available measurements in children and adults (including newborn infants). It therefore seems prudent to regard this report of fetal RBF as provisional until it is confirmed by further studies.

Sodium Excretion

The same data sources used to calculate fetal GFR[5,7] can also be used to calculate FE_{Na}, the proportion of filtered sodium excreted in the urine. FE_{Na} is the excretion rate of sodium divided by its filtration rate, which reduces to

$$FE_{Na} = \frac{U_{Na} \times P_{Cr}}{U_{Cr} \times P_{Na}} \times 100$$

In term infants, children, and adults with normal renal function on a normal sodium intake, FE_{Na} is less than 1%. As shown in Figure 2-4, FE_{Na} is high in the fetus until term, as well as in neonates before about 32 weeks' corrected gestational age, but in neonates from 33 weeks onward, it is "normal" (i.e., <1%). As with creatinine clearance, FE_{Na} is much higher in the fetus than in the infant after birth. These findings indicate that the fetal kidney, compared with that of the newborn infant after birth, is filtering and excreting sodium at a high rate. This is necessary to maintain the volume of the amniotic fluid that is constantly being swallowed and reabsorbed by the fetus. The consequences of failure of this replacement are well known (the Potter sequence).

Urinary Concentrating and Diluting Ability and Urine Flow Rate

No information is available as to the ability of the fetus to concentrate or dilute urine. The fact that urinary sodium concentration falls and that of nitrogenous substances such as urea and creatinine rises during the second half of pregnancy in fetuses with a good renal prognosis[7] suggests that the tubular transport processes that underlie the concentrating and diluting processes are developing during this period. It is likely that the capacity of the fetus to produce concentrated or dilute urine is similar to that of the prematurely born infant of a similar degree of maturity.

Fetal urine output has been measured by ultrasonography[6] and is remarkably high compared with that of the postnatal infant. The urine flow rate can be as high as 20% to 25% of GFR, a value never seen in extrauterine life except in extraordinary circumstances. Presumably, like the very high

FE_{Na} in these same infants, this reflects the need to produce amniotic fluid at a high rate to replace that ingested by the fetus. Recovery of the voided water and electrolytes via the infant's gastrointestinal tract and the ready access to virtually unlimited supplies via the placenta enable this high output to be maintained without the risk of ECF volume depletion, a situation that ceases to apply if the fetus is born very prematurely.

RENAL FUNCTION IN THE HUMAN INFANT BORN AT TERM

Glomerular Filtration Rate

GFR is low in newborn infants, even if a correction is made for body size. For historical reasons, the usual correction factor is body surface area (BSA), and GFR is most commonly expressed in terms of milliliters per minute (mL/min) per 1.73 m^2 BSA, even though a good case has been made for expressing it in relation to kilograms of body weight.[13] Numerous studies, using various methods including the clearances of inulin, mannitol, and creatinine, have shown that GFR at approximately postnatal week 1, after the transition from fetal to neonatal circulation has taken place, is about 2.5 to 5 mL/min in absolute terms, or 20 to 40 ml/min/1.73 m^2. This increases to about 50 mL/min/1.73 m^2 at 1 month, 60 at 3 months, 80 at 6 months, and 100 at 12 months. The adult value of about 120 mL/min/1.73 m^2 (range, 90 to 150 mL/min/1.73 m^2) is reached somewhere between the first and the second birthdays.[14-17] Normal values for GFR during the first 2 years of life are summarized in Table 2-1.

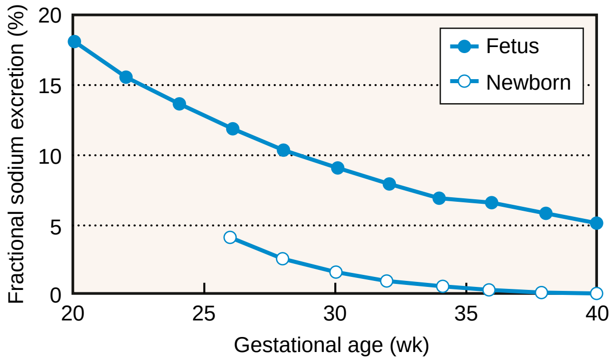

Figure 2-4 Fractional sodium excretion in fetuses (calculated as described in the text) and in newborn premature infants at comparable postconceptional ages. (Data from references 5 through 8.)

Formal measurement of GFR is laborious and is not often done for clinical purposes. The most widely used proxy measurement for GFR is the plasma creatinine concentration (P_{Cr}), which in a steady state is inversely proportional to GFR. In utero, the maternal and fetal blood are in equilibrium with respect to the concentration of small solutes such as creatinine,[5,18] and therefore, the infant's P_{Cr} at birth (e.g., in cord blood) reflects the mother's, not the baby's, renal function. In term infants, the P_{Cr} at birth is typically 70 to 90 μmol/L (about 1 mg/dL), falling to about half of this value by 1 week of age and remaining steady for the remainder of the first month. There is considerable variation among published series as to absolute values for P_{Cr}, mainly reflecting difficulties in laboratory measurement of P_{Cr} at the low concentrations typically observed in healthy infants. For modern methods giving a good approximation to "true" P_{Cr}, the mean stable concentration after the first week is about 30 μmol/L (0.3 mg/dL), with a range of 15 to 40 μmol/L (0.17 to 0.45 mg/dL).[19]

Renal Blood Flow and Filtration Fraction

RBF and renal plasma flow (RPF) are impossible to measure directly in healthy human infants. The renal clearances of para-amino hippurate (PAH) and the radiocontrast material diodrast have been widely used as an estimate of RPF, based on the assumption that these compounds are almost completely (>90%) extracted from renal arterial blood on a single passage through the renal circulation. Early measurements using these methods in babies gave very low values in relation to simultaneously measured GFR, yielding an average value for filtration fraction (GFR/RPF) of about 0.5, compared with a typical adult value of 0.2.[15,20] However, in one study, the renal extraction of PAH was measured directly in infants undergoing renal vein catheterization; the results showed clearly that PAH extraction is very incomplete in early infancy, and therefore that PAH clearance seriously underestimates RPF.[12] This is probably due to the fact that, as previously mentioned, the deeper (juxtamedullary) nephrons contribute most of the newborn infant's renal function. Postglomerular blood from this subpopulation of nephrons flows directly into the vasa recta system without perfusing the peritubular capillary plexus that supplies the proximal tubule, where PAH is extracted from the blood and secreted into the tubule lumen. When correction is

Table 2-1 Normal Values for Glomerular Filtration Rate during the First 2 Years of Life*

	Mean GFR (±2 SD)		
Age	**mL/min**	**mL/min/kg**	**mL/min/1.73 m^2**
1 wk	3.75 (2.5-5)	1.2 (0.8-1.6)	30 (20-40)
1 mo	6 (4-8)	1.5 (1-2)	50 (30-70)
3 mo	10.5 (7-14)	1.9 (1.2-2.4)	60 (40-80)
6 mo	18.5 (12.5-25)	2.4 (1.6-3.2)	80 (60-100)
1 yr	30 (20-40)	3 (2-4)	100 (75-125)
2 yr	45 (30-60)	3.3 (2.2-4.4)	120 (90-150)

*Values are presented uncorrected, factored by body weight, and corrected to a body surface area of 1.73 m^2. Data are pooled from multiple sources and rounded off to the nearest 2 or 3 significant figures.

GFR, glomerular filtration rate.

made for PAH extraction, filtration fraction in infants is similar to the adult value of 0.2,[12] indicating that RPF is about five times GFR. RBF is easily calculated from RPF and hematocrit.

Sodium Excretion

Healthy term infants are able to produce virtually Na-free urine (FE_{Na} much less than 1%).[8,21] The importance of this fact is difficult to overestimate. The baby fed on her or his mother's milk has a low Na intake, in the region of 1 to 1.5 mmol/kg daily, which is close to the amount needed for growth. Virtually all of this Na must therefore be retained. Conversely, many studies have shown that the ability to excrete an Na load is less well developed than in older individuals.[22] When this observation was first made, it was interpreted as meaning that renal function in the newborn was "immature"; however, it is unusual and unphysiologic for such an infant to be in a situation in which there is a need to excrete a salt load. In all but exceptional circumstances, the prime requirement of the neonatal kidney is conservation, not excretion, of Na.

Urinary Concentrating and Diluting Ability and Urine Flow Rate

The normal adult kidney can produce urine with an osmolality of greater than 1000 (typically 1200 to 1400) mOsm/kg H_2O. The healthy newborn infant who is subjected to water deprivation for 10 to 14 hours can achieve an osmolality of only 500 to 700 mOsm/kg.[23,24] This value increases gradually during the first few months and approximates the adult value by about 1 year of age (Fig. 2-5). However, it was shown many years ago that, in thirsted adults, about half of the solute contributing to urinary osmolality was urea, the remainder being electrolytes. Infants, being normally in a state of marked anabolism (growth), have a much lower urea production rate than adults and therefore have less need to produce highly concentrated urine in order to conserve water. Edelmann and colleagues[25,26] showed that, if the urea production rate of infants is increased toward that of adults by means of high protein feeding or addition of urea to the diet, even young infants can concentrate their urine almost as well as adults (Fig. 2-6). Here again, the casual assumption that the homeostatic needs of infants are the same as those of adults leads to incorrect interpretation of the results of tests of renal function. The capacity of the neonate to dilute urine, on the other hand, equals that of adults (minimum urine osmolality, <50 mOsm/kg H_2O).[27]

The factors determining urine flow rate (V) are the rate of generation of solute requiring urinary excretion and the capacity of the kidney to concentrate and dilute the urine with respect to plasma. Urinary solute has two main components: minerals (mostly Na, K, Cl, and P) and urea. If a healthy term infant were fed on his or her mother's milk at 150 mL/kg/day, the total potential solute content of the diet would be about 15 mOsm/kg/day. However, a large part of this content is retained and incorporated in new tissue: the actual solute load requiring excretion is in the range of 5 to 10 mOsm/kg/day.[28] Given that the infant can concentrate urine only to about 600 mOsm/kg H_2O, a solute production rate of 7.5 mOsm/kg/day necessitates a minimum urine volume of 12.5 mL/kg/day, approximately 0.5 mL/kg/hr, to avoid solute retention (i.e., uremia). This theoretical calculation agrees well with the clinical observation that, when newborn infants born at term were thirsted for 2 to 3 days after birth, their urine output was 0.3 to 0.5 mL/kg/hr.[29]

Given that sick infants are likely to be catabolic and therefore producing more solute for excretion than healthy ones, a urine flow rate of less than 1 mL/kg/hr suggests some form of renal insufficiency and is widely accepted as a criterion for the diagnosis of oliguric renal failure. Theoretically, the maximum urine output for the same solute load, assuming

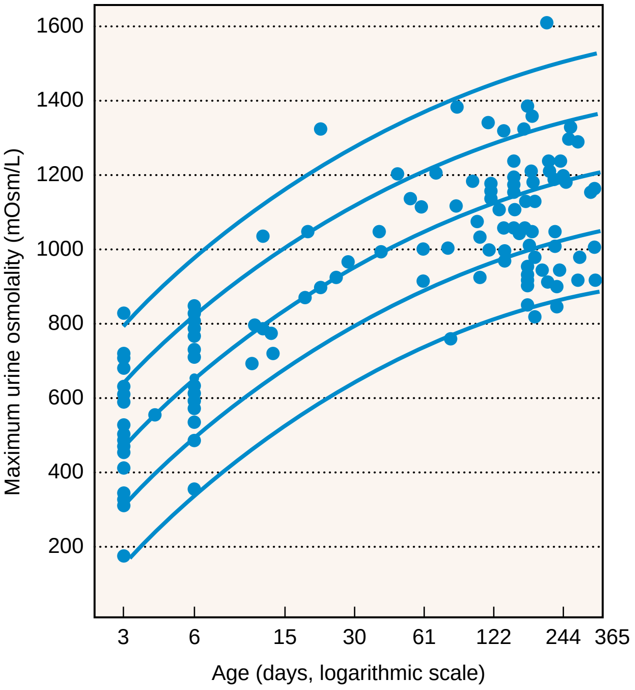

Figure 2-5 Range of normal values for maximal urine osmolality in response to dehydration during the first year of life. (Modified from Polacek E, Vocel J, Neugabauerova L, et al. The osmotic concentrating ability in healthy infants and children. *Arch Dis Child.* 1965;40:291-295.)

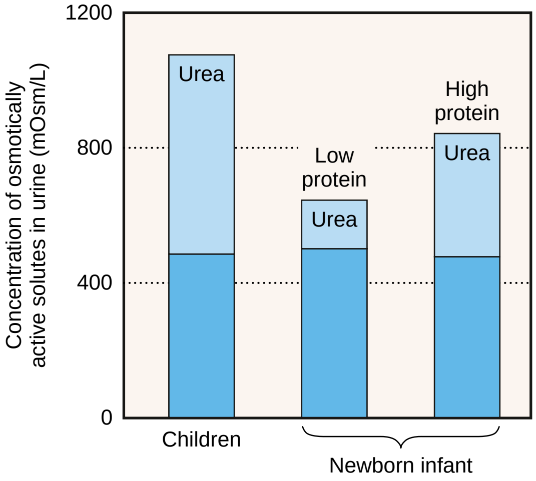

Figure 2-6 The effect of high and low protein feeding on the ability of newborn infants to concentrate urine. The infant fed a low-protein (physiologic) diet produces very little urea for excretion *(light shading)*. The darker shaded sections represent non-urea solute, mostly electrolytes. Note that the ability to concentrate non-urea solute is unaffected by the excretion rate of urea. (Redrawn with permission of the *Journal of Clinical Investigation* from Edelmann CM Jr, Barnett HL, Troupkou V. Renal concentrating mechanism in newborn infants: effect of dietary protein and water content, role of urea and responsiveness to antidiuretic hormone. *J Clin Invest.* 1960;39:1062-1069.)

a maximally dilute urine of about 40 mOsm/kg H_2O, would be 375 mL/kg/day, or about 15 mL/kg/hr, although this capacity is seldom, if ever, needed in normal circumstances. Between the limiting values of 1 and 15 mL/kg/hr, V is actually determined by water intake. Healthy infants, demand-fed on their mothers' milk, usually produce urine at about 3 mL/kg/hr, demonstrating that the ratio of solute to water in mature human breast milk is close to ideal for the needs of the infant.

Urinary Acidifying Capacity

Newborn infants can lower their urinary pH to values similar to those of healthy adults (<5.5).[30] The capacity to excrete an acid load depends on other factors as well as the ability to lower urine pH, notably the presence of urinary buffers (mainly inorganic phosphate and ammonium). The results of ammonium chloride loading tests in normal infants show that the maximal net acid excretion rate is comparable to the adult value if factored by GFR (i.e., expressed as micromoles hydrogen ion per 100 mL GFR). Because GFR is lower in infants than in adults, there is some reduction of maximal net acid excretion standardized to 1.73 m^2. In normal circumstances, this poses no problem for the infant, because the same strongly anabolic state that limits the urea production rate also leads to a relatively low production rate of nonvolatile acid requiring excretion by the kidney. Only if the child becomes sick and catabolic is the limited capacity to excrete hydrogen ions exposed, and in such circumstances (e.g., sepsis) infants develop metabolic acidosis relatively easily.

In health, the plasma bicarbonate concentration is normally equal to or just greater than above the renal bicarbonate threshold—the plasma concentration below which the urine is bicarbonate free and above which bicarbonaturia occurs. The threshold in normal adults is 25 to 27 mmol/L; in term newborns, it is a little lower, typically 22 to 24 mmol/L. The normal bicarbonate concentration is therefore slightly lower in healthy infants than in adults, and the results of blood electrolyte and gas analyses should be interpreted accordingly. A major determinant of the renal bicarbonate threshold is ECF volume. Newborn infants have an expanded ECF volume relative to adults, and this is the probable explanation for their low bicarbonate threshold and mild "hypobasemia."

Why Is Renal Function So Low in the Newborn Infant?

Healthy newborn infants are growing at a faster rate than at any other stage of life. The energy cost of this growth is high and must come entirely from mother's milk. The baby's mother is the exclusive source not only of the energy consumed in growth but also of the protein, minerals, and other dietary components that are needed to lay down new tissue.

As mentioned earlier, the main metabolic work performed by the kidney is active, energy-dependent reabsorption of Na by the tubule. In biologic terms, the "dyad" of breast-feeding mother and infant represents a single entity, an extension of the pregnant mother-fetus unit. Any unnecessary energy consumption by the breast-fed infant is a tax on the mother and, if food is not abundant, wasteful and potentially hazardous. The difference in GFR between a 1-month-old infant and an adult is about 70 mL/min/1.73 m^2. This corresponds to a difference in obligate Na reabsorption of 1.88 mol/day/1.73 m^2, requiring an energy expenditure of 6.8 kcal/day/1.73 m^2.[31]

Translated into neonatal terms, if the newborn infant had a GFR equivalent to that of the adult, an increase in energy consumption of about 3% of the basal metabolic rate would be required. This may seem a small amount, but in the subsistence conditions in which humans probably evolved, it is likely that this requirement would entail a significant selective disadvantage. Furthermore, the highly anabolic condition of the infant means that almost all ingested proteins and minerals are incorporated in new tissue, leaving very little solute remaining for excretion.[28] As a pioneer of developmental physiology put it, "Growth is the third kidney" (Fig. 2-7).[32] It can be seen, therefore, that the optimal level of renal function in the newborn infant is the minimum that meets the infant's limited excretory and homeostatic needs, whereas anything in excess of this would pose an unnecessary energy cost to the mother-baby dyad. The only negative consequence of low GFR for the infant is that, if growth ceases and she or he becomes catabolic, the increased rate of input of solute to the ECF could easily lead to metabolic derangement, as in the syndrome of late metabolic acidosis of prematurity.

RENAL FUNCTION IN THE PREMATURE HUMAN INFANT

Glomerular Filtration Rate

Measurement of GFR in premature newborn infants is difficult. Several studies have reported the clearance of creatinine, inulin, and other markers. However, the basic assumptions that underlie the clearance of a particular compound as a valid measure of GFR (free filtration at the glomerulus and absence of tubular reabsorption or secretion) have not been rigorously validated in tiny infants. For example, studies in newborn rabbits[33] suggest that there is significant tubular reabsorption (or backleak) of creatinine, which would lead to underestimation of true GFR. In addition, at least one report[34] has questioned whether inulin, usually taken as the "gold standard" marker for GFR, is fully filtered by the premature human glomerulus, although other studies appear to show convincingly that it is.[35] In any case, reports of inulin clearance in preterm infants are few. Notwithstanding these difficulties, numerous studies using various methods have given reasonably consistent results. GFR is typically 0.5 to 1 mL/min (about 10 mL/min/1.73 m^2) in babies of 28 to 32 weeks' gestation, measured during the first week of extrauterine life, and rises in an approximately exponential fashion from 32 weeks to achieve the value of 3 to 5 mL/min (about 30 mL/min/1.73 m^2)

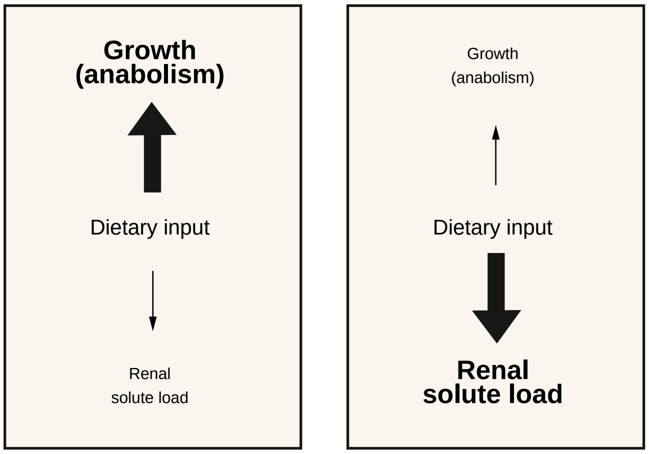

Figure 2-7 The inverse relationship between growth and the rate of generation of urinary solute for excretion, assuming a constant dietary input.

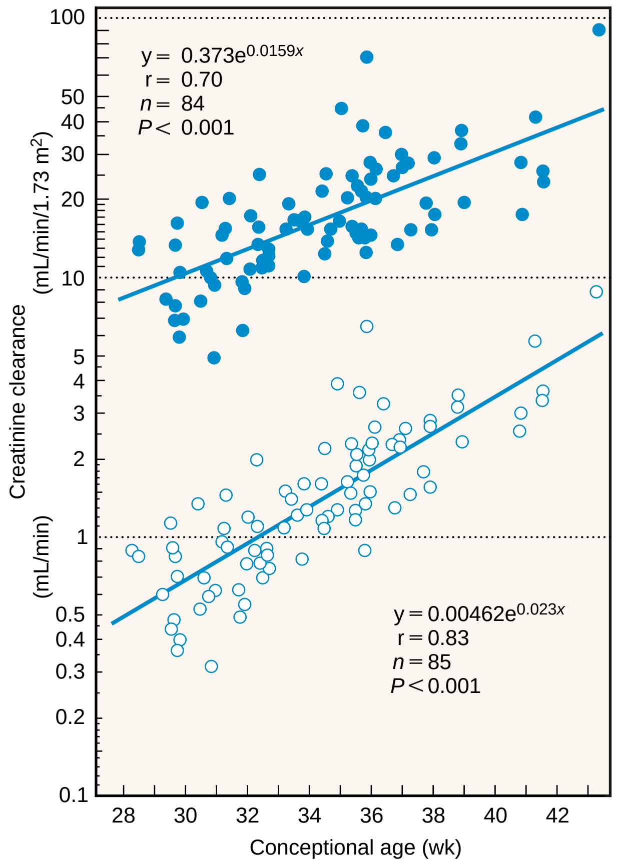

Figure 2-8 Glomerular filtration rate, measured as creatinine clearance, in newborn infants from 28 to 42 weeks' gestational age. The filled circles and upper regression line represent GFR expressed as mL/min/1.73 m^2, and the open circles and lower regression line represent GFR uncorrected for body size (mL/min). The scale on the Y axis is logarithmic. (Redrawn from Al-Dahhan J, Haycock GB, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates. I. Renal aspects. *Arch Dis Child.* 1983;58:335-342.)

at 40 weeks.[8] Normal values of GFR, both uncorrected and corrected for BSA, are shown in Figure 2-8.

Several studies have proposed that premature and term infants follow different patterns of postnatal development of GFR. In general, these reports have lumped together preterm infants across a wide range of gestational ages and compared them, as a group, with term infants. However, if infants born at different stages of gestation are compared at the same absolute or postconceptional age, they follow similar tracks, once they have passed the transitional period of adjustment to the change from intrauterine to extrauterine life (the first few postnatal days).[8,36] For example, two groups of infants with identical postconceptional ages (245 ± 23 and 247 ± 19 days, respectively) had identical GFR, both corrected and uncorrected for BSA, even though the first group were studied at 5 to 6 days postnatal age and the second at 26 to 68 days.[8] This is consistent with the observation, based on careful postmortem studies, that preterm infants with weights appropriate for gestational age who died in the first year of postnatal life had the same complement of nephrons as term infants.[37]

Conversely, LGA infants born with a diagnosis of intrauterine growth retardation have smaller kidneys and higher blood pressure,[38] as well as significantly reduced nephron numbers, compared both with term controls and preterm infants born at weights appropriate for gestational age.[37,39,40] This may have important adverse long-term consequences in predisposing to the development of essential hypertension[41] and possibly non–insulin-dependent diabetes mellitus.[42] It seems reasonable to predict that LGA infants, if studied in the neonatal period (or later), might have lower GFR than their appropriate for gestational age counterparts. No study has yet addressed this specific point. Given that the differences are probably relatively small, and given the difficulty of measuring GFR accurately in small infants, it is doubtful whether this point is amenable to direct clinical investigation.

The figures for GFR in preterm infants previously cited refer to well babies. Not surprisingly, sick babies have been shown to have reduced renal function compared with healthy, equally premature controls, especially if they are hypoxic or hypotensive or if they are receiving mechanical ventilatory support.[43]

Renal Blood Flow and Filtration Fraction

Measurement of RBF is even more difficult in small infants than measurement of GFR. In animal studies, a progressive rise in RBF with development has been observed, in parallel with the increase in GFR. Studies in piglets (Fig. 2-9) showed that this rise is determined primarily by a fall in renal vascular resistance rather than by a rise in perfusion pressure.[44] Anatomic and physiologic investigations in several species have shown that the deep (juxtamedullary) nephrons, which are the first to be formed, are preferentially perfused during early development and that more recently formed glomeruli are recruited centrifugally.[45-47] The most superficial (subcapsular) glomeruli, which are formed at 34 to 36 weeks in the human,[4] are the last to function.

Although direct evidence is not available in humans, the pattern in other species, from rodents to nonhuman primates, is so consistent that it is overwhelmingly likely that the same sequence occurs in babies. That is, the relatively low RBF and GFR that characterize the very premature infant result from the fact that only the deepest and ontologically oldest glomeruli are perfused and filtering, the more superficial ones being vasoconstricted. The single study that has estimated RBF in human fetuses by color pulsed wave Doppler ultrasonography gave values for two kidneys increasing from 40 mL/min at 22 weeks to 130 mL/min at 40 weeks.[10] However, these results cannot be extrapolated directly to the postnatal environment, because there are good reasons to believe that there are important differences in renal function between fetuses still in utero and prematurely born infants of the same gestational age, as discussed in a later section of this chapter.

Sodium Excretion

Investigations from several groups[8,48,49] have consistently shown that infants born at or after 32 to 33 weeks' gestation can produce virtually Na-free urine, equivalent to an FE_{Na} of much less than 1% of the filtered load, from the first few days of life. Infants born before 32 weeks are less efficient in this respect, and during their first 2 weeks of extrauterine life FE_{Na} is high, often greater than 1%, with the most immature infants having the highest values (Fig. 2-10). FE_{Na} values of 5% or even higher are seen in some infants born at 26 to 28 weeks.[8,50] In consequence, with a dietary Na intake in the range of 1.3 to 1.5 mmol/kg/day (equivalent to that provided by mature human milk), which is sufficient to allow for normal growth

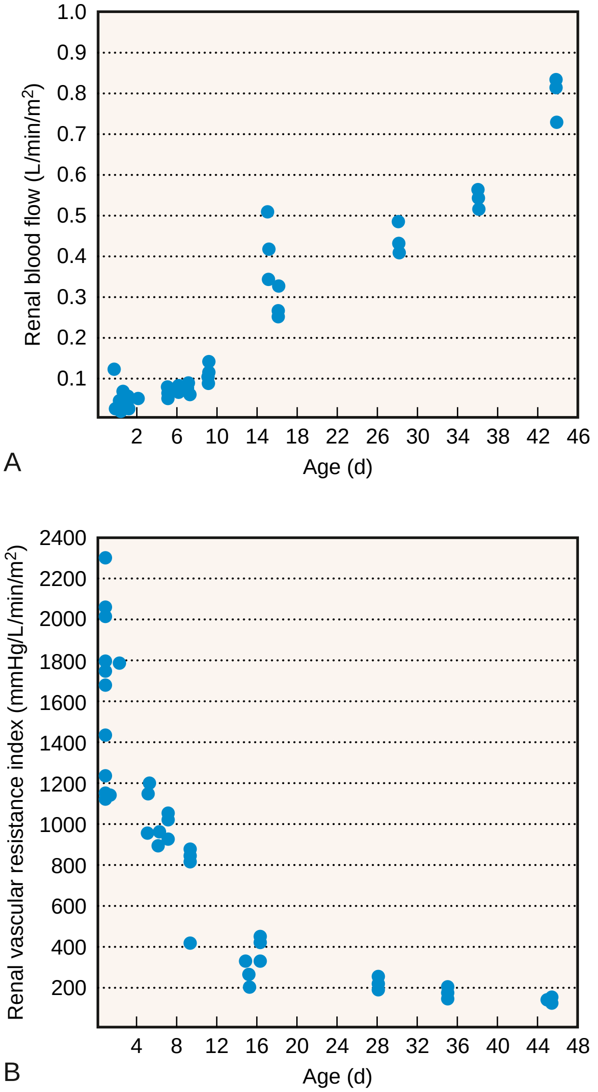

Figure 2-9 Change in renal blood flow **(A)** and renal vascular resistance **(B)** with postnatal age in piglets. (Redrawn from Gruskin AB, Edelmann CM Jr, Yuan S. Maturational changes in renal blood flow in piglets. *Pediatr Res.* 1970;4:7-13.)

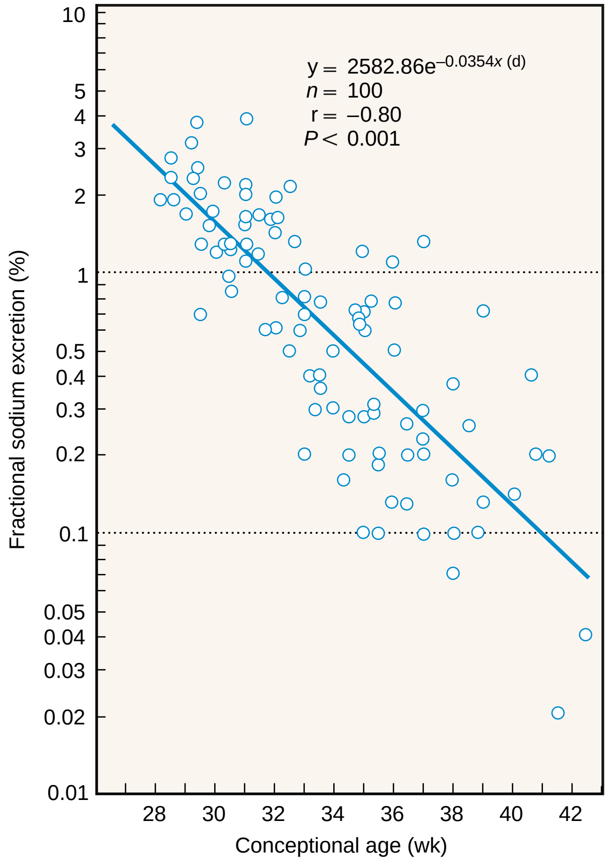

Figure 2-10 Fractional sodium excretion plotted against postconceptional age in newborn infants from 23 to 42 weeks' gestational age. The scale on the Y axis is logarithmic. (Redrawn from Al-Dahhan J, Haycock GB, Chantler C, Stimmler L. Sodium homeostasis in term and preterm neonates: I. Renal aspects. *Arch Dis Child.* 1983;58: 335-342.)

and development in term infants, these very immature babies would be in negative Na balance for up to 10 to 14 days.[51] This situation commonly leads to the development of hyponatremia by the second or third week of life (late hyponatremia of prematurity).[8,52-54]

It has been argued that this hyponatremia is caused by excessive water intake and is therefore dilutional. If this explanation were correct, the logical response would be to restrict water intake, and one study showed that this approach is effective in preventing late hyponatremia.[55] However, there are good reasons for believing that salt supplementation is a more physiologic method of maintaining plasma Na concentrations within the normal range. First, if the intrauterine pattern of growth and development is taken as the optimum model for extrauterine care of the very premature infant, providing high throughput of salt and water, which leads to moderate volume expansion, would seem preferable to inducing volume contraction by restricting the intake of both. Second, in very premature infants who are not given supplementary Na, the renin-angiotensin system is strongly activated, suggesting volume contraction, and this activation is suppressible by Na supplementation in an amount calculated to replace urinary losses (Fig. 2-11).[56] Third, supplemented infants regain their birth weight more rapidly than unsupplemented controls, and this advantage is maintained after the salt supplement is withdrawn,[57,58] which suggests that the enhanced weight gain is not just ECF expansion due to salt and water overload (Fig. 2-12). Finally, there is experimental and clinical evidence that sodium depletion in the neonatal period in premature animals and infants has long-term, and possibly permanent, adverse effects on tissue growth of many organs including the central nervous system.[59,60] It is noteworthy that even the most premature infants (born before 30 weeks) are able to produce Na-free urine by the end of the second extrauterine week and thereafter maintain normonatremia and satisfactory growth and weight gain on the same relatively low Na intake as infants born at or near term.

The weight of evidence therefore favors the provision of supplementary Na to a total input of 4 to 5 mmol/kg/day from the third or fourth postnatal day until the end of the second week, after which breast milk (or an artificial formula of suitable composition) may safely be substituted. These recommendations apply to well, very preterm infants; babies who are sick, especially if they are hypoxic, may lose even greater amounts of Na in the urine.[43] It is not possible

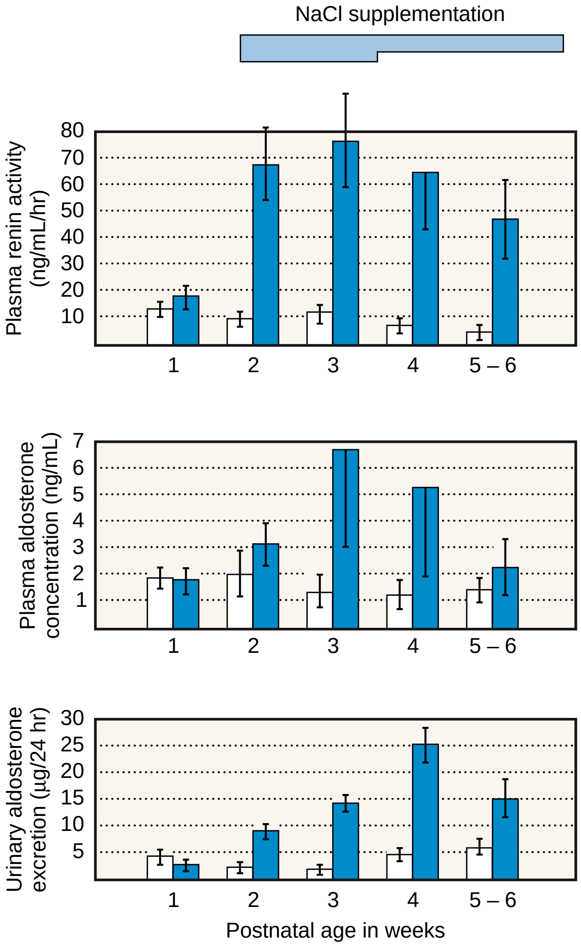

Figure 2-11 Postnatal changes in plasma renin activity, plasma aldosterone concentration, and urinary aldosterone excretion rate in premature infants. The high levels shown by the shaded bars are those found in infants with a low sodium intake (<1.5 mmol/kg/day). The postnatal rise in renin and aldosterone levels was fully suppressed by salt supplementation beginning at 2 weeks' postnatal age *(open bars)*, suggesting that the rise is a response to extracellular fluid volume contraction. For the first two weeks, sodium supplements were given at 3-5 mmoL/kg/day *(thick bar)* then halved for the remainder of supplementation period *(thin bar)*. (Redrawn from Sulyok E, Németh M, Tenyi I, et al. Relationship between the postnatal development of the renin-angiotensin-aldosterone system and the electrolyte and acid-base status in the sodium chloride supplemented premature infant. *Acta Paediatr Acad Sci Hung.* 1981;22:109-121.)

to recommend a single, generally applicable salt intake for such babies; their plasma electrolyte concentrations should be monitored frequently, and Na intake adjusted accordingly, until their clinical condition improves. The use of furosemide and other powerful diuretics, not uncommonly prescribed for premature infants with respiratory problems, obviously exacerbates the tendency to Na loss and hyponatremia, and attention must be paid to this consequence of their administration.

Why Is Sodium Reabsorption Inefficient in the Premature Infant?

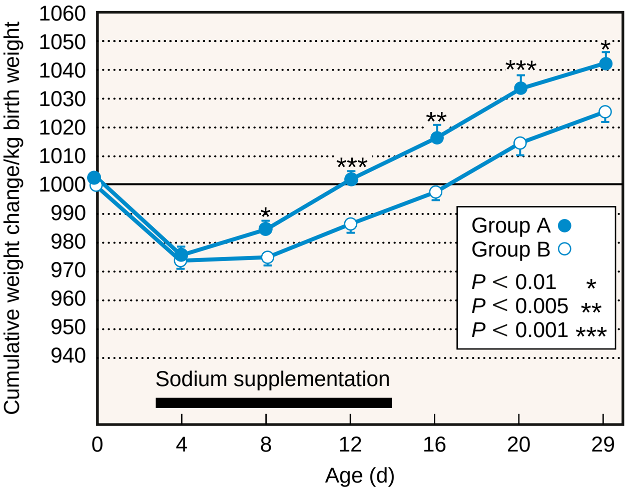

Figure 2-12 Postnatal change in weight expressed per kilogram of birth weight in premature infants receiving *(solid circles)* and not receiving *(open circles)* salt supplementation from the 4th to the 14th postnatal day. Note that the difference between the two groups persists beyond the end of the period of supplementation. (Redrawn from Al-Dahhan J, Haycock GB, Nicol B, et al. Sodium homeostasis in term and preterm neonates: III. The effect of salt supplementation. *Arch Dis Child.* 1984;59:945-950.)

Sodium is actively reabsorbed in all tubular segments except the descending limb and the thin part of the ascending limb of the loop of Henle. In the adult, about 65% of filtered Na is reabsorbed in the proximal tubule, about 25% in the TAL, and the remaining 9% to 10% in the distal convoluted tubule and collecting duct. Clearance studies have shown that the proximal tubule accounts for a smaller fraction of total Na reabsorption in infants than in adults[27] and that this fraction is even less in the premature than in the term infant (Fig. 2-13).The energy-consuming step in tubular Na reabsorption is the extrusion of Na from the epithelial cell interior into the peritubular fluid and hence into the blood perfusing the peritubular capillary plexus. This process depends on the enzyme sodium-potassium adenosine triphosphatase (Na^+,K^+-ATPase), which is located in the basolateral (outer or antiluminal) cell membrane.

Studies in developing rats have shown that the capacity to reabsorb fluid in the proximal tubule is correlated with basolateral cell membrane area. Other studies by the same investigators showed that the amount of Na^+,K^+-ATPase in the tubule is low in early gestation and increases with maturation, and that the rate of increase in expression of the enzyme is augmented by antenatal exposure to glucocorticoid.[61] The accelerated development of Na reabsorption that occurs in the human premature infant after delivery is accompanied by a parallel increase in the amount of Na^+,K^+-ATPase present in the red blood cells,[62] suggesting that delivery provides a stimulus to maturation of the enzyme, probably associated with an increase in the area of the basolateral membrane where the enzyme is located and where active Na transport takes place. This stimulus may well be a surge in endogenous glucocorticoid (cortisol) secretion, which is well known to occur after delivery. The probability that glucocorticoid plays an important role in this process is further supported by the observation that tubular Na reabsorption was more advanced in prematurely born human infants whose mothers had been treated with dexamethasone than in those whose mothers were not so treated.[63]

The available evidence may be summarized as follows: During later fetal development (26 weeks to term), there is progressive growth of the proximal tubule and increased expression of Na^+,K^+-ATPase in the basolateral membrane.

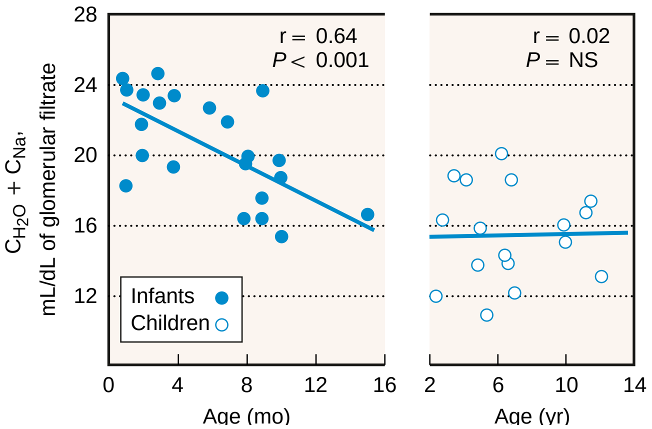

Figure 2-13 Proportion of filtered sodium escaping reabsorption in the proximal tubule (i.e., delivered to the distal tubule) in infants (*solid circles* and regression line) and in children (*open circles* and regression line) of various ages. The studies were performed in maximal water diuresis, in which the sum of sodium clearance (C_{Na}) and free water clearance (C_{H2O}) represents the amount of sodium delivered to the distal nephron beyond the loop of Henle. (Redrawn from Rodriguez-Soriano J, Vallo A, Oliveros R, Castillo G. Renal handling of sodium in premature and full-term neonates: a study using clearance methods during water diuresis. *Pediatr Res.* 1983;17:1013-1016.)

Consequently, there is a progressive increase in the proportion of filtered Na that is reabsorbed in that part of the tubule. In the very premature infant, the relative lack of function in the proximal tubule cannot be adequately compensated by increased Na reabsorption in more distal segments, and urinary Na wasting occurs. From about 32 weeks' gestation onward, enhanced reabsorption of Na in the distal tubule compensates for the relative proximal tubular Na rejection, and urinary Na wasting is prevented. This increased distal Na reabsorption is mediated by aldosterone, levels of which are high in the newborn period at all gestational ages; however, only in more mature infants is the urinary Na^+/K^+ ratio correlated with plasma aldosterone concentration, suggesting that the immature tubule is unable to respond to mineralocorticoid appropriately. Na reabsorption in the TAL appears to be well developed early in gestation, because even very preterm infants can dilute the urine efficiently in response to water loading,[27,64] a process that depends on Na reabsorption without water in the TAL and early distal convoluted tubule (the diluting segment). Maturation of the proximal tubule is accelerated after delivery, probably due to glucocorticoid secretion, which explains the observation that preterm infants of more than 2 weeks' postnatal age show a more advanced pattern of tubular Na reabsorption than do infants of the same postconceptional age but less than 10 to 14 days postnatal age.

Urinary Concentrating and Diluting Ability and Urine Flow Rate

Premature infants have an even more limited capacity to concentrate their urine than those born at term, with a maximum urine osmolality of about 500 mOsm/kg H_2O.[23] Furthermore, the osmotic threshold for release of antidiuretic hormone appears to be higher in preterm infants (plasma osmolality ≈ 290 mOsm/kg H_2O) than in term infants (plasma osmolality ≈ 282 mOsm/kg H_2O).[24] This means that premature infants do not begin to concentrate their urine until they are significantly more dehydrated than term infants, and that at any degree of dehydration, as measured by plasma osmolality, preterm infants produce less concentrated urine than term infants and are therefore more vulnerable to hypernatremia and hyperosmolality. Historically, when deprived of fluid for up to 72 hours (an intervention absolutely contraindicated in modern clinical practice!), preterm infants reduced their urine flow rate to approximately 1 mL/kg/hr, about twice that observed in term babies.[29]

Diluting ability, by contrast, is well developed even in very premature infants, who can dilute their urine to 40 to 50 mOsm/kg H_2O,[27] a value similar to that for term infants and indeed for adults, who can adjust urinary water excretion appropriately in response to changes in intake.[64] As mentioned in the previous section, this implies that the generation of solute-free water in the TAL of the loop of Henle is well established quite early in gestation. This diluting capacity is blunted in the presence of antidiuretic hormone release, whether osmotically mediated (dehydration), nonosmotically mediated (hypovolemia or hypotension), or truly inappropriate (e.g., after intracranial hemorrhage or perhaps secondary to positive-pressure ventilation). In practice, well-hydrated premature infants typically have a urine flow rate of 2 to 3 mL/kg/hr, with a limiting range of about 1 to 10 mL/kg/hr.

The limited urinary concentrating capacity of newborn infants, compared with adults, is a result of multiple factors. First, the loops of Henle are shorter than in later development. The loop of Henle and its associated microvasculature (the medullary vasa recta system) act as a countercurrent multiplier and exchanger system, leading to a progressive rise in medullary interstitial osmolality as the papillary tip is approached. Theoretical analysis of the physics of such systems shows that the efficiency of the resulting osmolar multiplication is a function of the length of the tubules that compose the mechanism. Second, the limited availability of urea, which contributes in a unique way to the osmolality of concentrated urine, restricts the extent to which urine can be concentrated when the infant is on a low-solute diet and in a state of anabolism (growth). The importance of urea was shown in a clinical study in which the addition of urea to the diet of premature infants increased urinary concentrating capacity by an additional 200 mOsm/kg H_2O.[25] In general, because of the limited capacity of newborn infants to reduce water excretion, especially if preterm, it is very important to ensure that their water intake is sufficient to allow them to maintain normal body fluid tonicity. This applies especially in the case of sick infants, in whom the rate of addition of solute to the ECF may be increased because of interruption of growth.

Urinary Acidifying Capacity

Even very preterm infants can lower their urine pH to a level that would be adequate to prevent acidosis in older individuals in most circumstances (urine pH <5.5).[65] However, the defense against systemic acidosis depends on factors other than this, and the preterm infant is therefore more vulnerable to disorders of acid-base balance than more mature subjects are. For an adult to excrete the amount of nonvolatile acid (acid other than carbonic acid) produced by normal metabolism, the urine must contain adequate amounts of buffers. The two main buffers are inorganic phosphate and ammonium. Preterm infants excrete very little phosphate, especially if breast fed, because the requirement for phosphate needed for bone mineral formation equals or even exceeds the dietary supply. For this reason, phosphate supplements are often given to prevent rickets, and an unintended benefit of this practice may be an increase in the supply of urinary buffer. Ammonium is synthesized by the renal tubules in response to

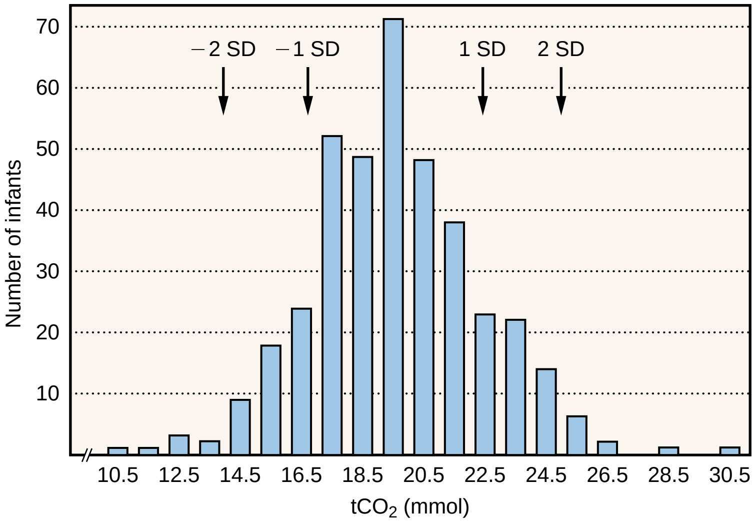

Figure 2-14 Distribution of plasma total carbon dioxide (tCO_2) concentration in premature infants during the first week of postnatal life. (Redrawn from Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. Late metabolic acidosis: a reassessment of the definition. *J Pediatr.* 1979;95:102-107.)

chronic acidosis, and preterm infants can synthesize ammonium quite well, but the maximum capacity to excrete hydrogen ions is nevertheless lower than that of term infants or older individuals when related to body weight. This is partly due to low GFR.

The most abundant nonvolatile acid that must be excreted in the urine is sulfuric acid, which is derived from the catabolism of sulfur-containing amino acids. In the strongly anabolic state that is normal for all growing infants, including those born prematurely, virtually all the dietary protein is incorporated into new tissue, and little or no sulfuric acid is formed. The low bicarbonate threshold seen in healthy term infants, referred to previously, is exaggerated in preterm infants. In a study of healthy, thriving preterm infants, the mean threshold was found to be 19 to 20 mmol/L (Fig. 2-14).[65] As with term infants, this is probably a consequence of expanded ECF volume, which is even more marked in the preterm than in the full-term infant.

Although the renal acidifying capacity of the preterm infant is sufficient for his or her normal needs, there is little reserve available to deal with unphysiologic demands. Metabolic acidosis occurs readily in preterm infants in two circumstances: when they become sick and therefore catabolic, and when the dietary load of potential nonvolatile acid is inappropriately high. In the 1960s, when modern neonatology was on an early segment of its learning curve, very-low-birth-weight infants were often fed very high protein diets, sometimes as much as 3 to 5 g/kg/day, in the belief that this would improve growth. One consequence was the generation of more sulfuric acid than the immature kidneys could excrete, leading to the syndrome of late metabolic acidosis of prematurity.[66] In this condition, babies appeared to do well for the first week or two, but then became unwell with interruption of weight gain and metabolic acidosis. The disorder then became self-perpetuating: the acidosis prevented growth and further increased the input of acid into the ECF. It was found that either reducing the protein content of the feed or treating the acidosis with alkali was curative; once the protein intake had been reduced to physiologic amounts, a single dose of bicarbonate was often enough to restore normal growth and prevent recurrence of acidosis.[66]

Because of changes in nutritional practice, the full-blown syndrome of late metabolic acidosis is now seen only occasionally. However, borderline late metabolic acidosis may be more common than is recognized. It has been reported that babies who are excreting maximally acid urine, although not acidotic by standard age-adjusted criteria, may thrive less well than those with higher urine pH, and that weight gain may be improved by alkali, suggesting that these infants are operating at the limit of their acid excretory capacity.[67,68] This possibility deserves exploration in preterm infants with poorer than expected weight gain for which other explanations are lacking.

RENAL FUNCTION IN CHILDHOOD

The topic of renal function in childhood is covered in detail in Chapter 3. The following paragraphs summarize the main features.

Glomerular Filtration Rate

By the age of 2 years, GFR factored by body surface area has reached adult values, and there is no significant or consistent change with age throughout childhood. The mean value is about 120 mL/min/1.73 m^2, with a range of about 85 to 145 mL/min/1.73 m^2. Because rates of creatinine production and creatinine excretion must be equal in a steady state, and because creatinine production is a function of muscle mass and therefore of body size, a useful approximation to GFR across the age range of 2 to 18 years can be obtained by the following formula:

$$\text{GFR} = \frac{\text{k} \times \text{Height}}{\text{Plasma creatinine}}$$

where GFR is expressed in mL/min/1.73 m^2 and Height in centimeters; k is 40 if the creatinine concentration is in micromoles per liter (μmol/L), and 0.45 if it is in milligrams per deciliter (mg/dL).[69,70] When the creatinine concentration is expressed in μmol/L, a quotient (height/creatinine) greater than 2.1 indicates a 95% probability that GFR is normal, and a quotient of less than 1.5 suggests a 95% probability of reduced GFR.[71] If the quotient lies between these two values, GFR should be measured by a more accurate method.

Other Aspects of Renal Function

RPF is proportional to GFR throughout childhood, with an average filtration fraction (GFR/RPF) of 0.2 (i.e., GFR is about 20% of RPF). Likewise, tubular function bears the same relation to GFR as in adults. The capacity to concentrate and dilute the urine is equal to that of the adult, as is the ability to excrete nonvolatile acid per unit of GFR.

RENAL FUNCTION IN THE ADULT

Renal function in the adult is covered in detail in standard textbooks of adult urology and nephrology. A few brief points are mentioned here.

In young, healthy adult men, the mean GFR, as measured by inulin clearance, is 127 ± 21 mL/min/1.73 m^2 (normal range, 85 to 170), and in women it is 118 ± 14 mL/min/1.73 m^2 (normal range, 90 to 145).[72] However, several studies have demonstrated that there is a progressive decline in both nephron number[1,2] and GFR[73] with age, the latter decline being measurable from about 40 years of age onward. The correlation between nephron number and age is weak but statistically significant. The weakness of the correlation results from the very wide scatter of individual values, which raises the possibility that the decline is not inevitable but may affect only a subpopulation of individuals and may be related to factors such as blood pressure, unrecognized renal disease, and diet. The mean GFR falls to about 70 mL/min/1.73 m^2 by the age of 90 years, again with a very wide scatter of individual values. Also, the gender difference in GFR seen in young adults disappears after the age of about 40 years. There are comparable changes in tubular function with advancing age, but in general these values remain proportional to GFR, and the overall decline in renal function probably reflects a reduction in total nephron number rather than failure of any particular aspect of tubular function. Renal function and disease in the elderly is the subject of a book by Macías-Núñez and Cameron[74] and of a review chapter by the same authors in a standard textbook of renal medicine.[75]

The formula given earlier for rough estimation of GFR from creatinine in children has not been validated and should not be used in adults. A number of formulas have been produced to achieve the same estimation in adults, and these were reviewed in a recent article.[76] The most satisfactory one, which also gives an estimate corrected for BSA, is the abbreviated Modification of Diet in Renal Disease (MDRD) study group formula,[77] which incorporates plasma creatinine concentration, age, gender, and ethnicity:

$$\text{eGFR} = 186.3 \times (0.011312 \times P_{Cr})^{-1.154} \times \text{Age}^{-0.203} \\ \times\ 0.742\ (\textit{if female}) \times 1.212\ (\textit{if black})$$

where eGFR is the estimated GFR (mL/min/1.73 m^2), P_{Cr} is the plasma creatinine concentration (μmol/L), and age is given in years.

REFERENCES

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CHAPTER 3

RENAL FUNCTION, FLUIDS, ELECTROLYTES, AND NUTRITION FROM BIRTH TO ADULTHOOD

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The majority of hospitalized pediatric patients with urologic disorders require the proper administration of intravenous fluid and nutrition. Fluid management is the most important treatment for patients during an acute episode of dehydration or sepsis, as well as during perioperative care. In the postoperative period, patients may develop problems unrelated to the genitourinary abnormality for which they were admitted that require long-term administration of intravenous fluid and parenteral nutrition. This puts them at a high risk for metabolic complications. The surgeon must recognize these electrolyte and metabolic derangements early to avoid potential complications.[1]

Genitourinary abnormalities in children are primarily congenital in origin, manifesting with either urinary tract obstruction or urinary tract infection. Fluid management in this group of children is based on a set of physiologic and biochemical principles that differ quantitatively and qualitatively from those used in adults. Children, and especially neonates and infants, are more prone to develop significant fluid and electrolyte losses that are related to their metabolism.[2] When normal intake ceases, their higher metabolic rate causes fluids and electrolytes to be lost faster, and their lower glomerular filtration rate (GFR) limits their ability to respond to dehydration and solute loss.[3,4] Of equal importance, the smaller lean body mass of infants and children reduces the quantitative error that is allowable in calculating fluid and electrolyte replacement without causing significant iatrogenic injury.[1] This chapter focuses on the understanding of renal function and fluid, electrolyte, and nutrition status in the pediatric surgical patient.

RENAL FUNCTION

The kidneys function to excrete water, solutes, and metabolic wastes in order to maintain a homeostatic internal environment despite fluctuations in diet and fluid balance. The integrity of cells depends on the osmolality of the extracellular fluid (ECF). This is kept under tight control through osmoreceptors and volume receptors that allow the brain and kidneys to produce hormones and vasoactive substances to regulate salt and water excretion. The kidneys receive 20% of the cardiac output. Each nephron receives the ultrafiltrate of plasma, which passes through the Bowman space into the renal tubule. More than 99% of the filtered water, sodium, chloride, and bicarbonate is reabsorbed by the renal tubules and returned to the plasma. Failure to reabsorb virtually all the sodium can result in life-threatening hyponatremia and volume depletion.

The rate of formation of the ultrafiltrate is the GFR, which is calculated from cardiac output and renal plasma flow. GFR is an important measure of renal function. Calculation of GFR is required in situations indicative of renal disease, such as abnormal urinary findings, peripheral edema, or hypertension. GFR in newborn term and preterm infants is less than that in adults.[5] In the term infant, GFR is approximately 21 mL/min/1.73 m^2, rising to 90 mL/min/1.73 m^2 by 2 weeks of age. GFR reaches adult levels (120 mL/min/1.73 m^2) by 1½ to 2 years of age. In addition, the concentrating capacity of preterm and full-term infants is well below that of adults. Infants have immature collecting tubules, which do not allow for adequate response to antidiuretic hormone (ADH). Consequently, during an episode of water deprivation, an infant can increase osmolarity to a maximum of only 900 mOsm/kg, whereas an adult can concentrate urine to 1200 mOsm/kg. The newborn excretes very dilute urine. Term infants have a diminished capacity to excrete excess sodium compared to adults. This factor is thought to be a tubular defect. Uniquely, premature infants are termed "salt wasters"; even during sodium restriction, they excrete high amounts of sodium. (See Chapter 2 for a more detailed discussion.)

In the clinical setting, GFR can be estimated by measuring serum creatinine, a metabolic end product of normal muscle metabolism. Creatinine is produced at a constant level and therefore is excreted proportionally to the GFR. In children, creatinine excretion is 15 mg/kg/day, and in adults, it is 20 mg/kg/day. This discrepancy reflects the increase in muscle mass as children age and grow. In addition, males have a higher serum creatinine concentration than females because of their increased muscle mass. Creatinine provides a 10% to 20% overestimate of GFR, because it is freely filtered at the glomerulus but also is secreted into the renal tubules. In patients with abnormal renal function, the degree of overestimation increases, because a larger amount of creatinine is being secreted. However, the creatinine clearance ratio can be used to monitor renal function in patients with renal failure. Creatinine clearance (C_{Cr}, expressed in milliliters per minute) is calculated from the following formula:

$$C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$$

where U_{Cr} is the urine creatinine concentration (mg/dL), P_{Cr} is the plasma concentration (mg/dL), and V is the urine flow rate (mL/min).

A 24-hour urine collection is needed to determine creatinine clearance but is often impossible to obtain in the pediatric population. Because of the limitations of serum creatinine and creatinine clearance, other diagnostic alternatives have been studied to produce a reliable and easy marker for monitoring pediatric GFR. A novel serum marker to measure kidney function is cystatin C. Cystatin C is a cysteine protease inhibitor that is made at a stable rate by most nucleated cells and can be measured in serum. Cystatin C does not depend on muscle mass, age, or gender, unlike serum creatinine.[6] A meta-analysis comprising approximately 4500 subjects found that cystatin C is a more accurate measurement of GFR than serum creatinine.[7] In 2004, the U.S. Food and Drug Administration

Table 3-1 Normal Caloric Requirements in Infants

Activity	Caloric Requirement (kcal/kg/24 hr)
Resting expenditure	50
Intermittent activity	15
Mild cold stress	10
Total maintenance	75

Adapted from Hensle TW. *Metabolic Care of the Neonate and Infant with Urologic Abnormalities: Clinical Pediatric Urology*. Philadelphia: WB Saunders; 1985.

Table 3-2 Energy Expenditure in Children

Body Weight (kg)	Energy Expenditure (per 24 hr)
3-10	100 kcal/kg
10-20	1000 kcal + 50 kcal/kg >10 kg
>20	1500 kcal + 20 kcal/kg >20 kg

Table 3-3 Daily Calorie and Protein Requirements in Infants and Children

Age (yr)	Caloric Requirement (kcal/kg BW)	Protein Requirement (g/kg BW)
0-1	90-120	2.0-3.5
1-7	75-90	2.0-2.5
7-12	60-75	2.0
12-18	30-60	1.5
>18	25-30	1.0

Adapted from Teitelbaum DH, Coran AG. Perioperative nutritional support in pediatrics. *Nutrition*. 1998;14:130-142.
BW, body weight.

Table 3-4 Fluid Requirements in Infants and Children

	Body Weight (kg)	Fluid Requirement (per 24 hr)
Premature	<2	150 mL/kg
Neonates and infants	2-10	100 mL/kg
Infants and children	10-20	1000 mL + 50 mL/kg >10 kg
Children	>20	1500 mL + 20 mL/kg >20 kg

Adapted from Teitelbaum DH, Coran AG. Perioperative nutritional support in pediatrics. *Nutrition*. 1998;14:130-142.

approved cystatin C as an alternative measure of renal function.[8] Further studies are needed to evaluate the utility of cystatin C in the pediatric population as a replacement for serum creatinine to measure GFR.

BODY COMPOSITION

Homeostasis within the body involves coordinated actions among complex hormonal, neuronal, vascular, renal, and behavioral mechanisms. To manage such a system, one requires a baseline understanding of its composition. Especially in surgical patients, monitoring of fluid balance enables the clinician to determine the clinical course of the patient.

Between 55% and 72% of the total body mass is water.[9] This percentage varies with age, gender, and fat content (water content in fat is low). In a term newborn infant, total body water accounts for 70% to 75% of the body weight. This decreases to 75% in infants and 70% in children, and decreases further to 60% in the adult male and 55% in the adult female. Requirements for water are related to caloric consumption. Therefore, the daily water requirement in infants and children is three times that in adults.

Body water is in a state of osmotic equilibrium between the intracellular and the extracellular space. Approximately two thirds of total body water resides in the intracellular fluid and approximately one third in the ECF. The ECF is composed of plasma, interstitial fluid, and transcellular fluid, which consists of pleural, peritoneal, and synovial fluids.[10] Venous circulation accounts for 85% of the vascular compartment, whereas the arterial side makes up 15%. In infants, the ECF constitutes an even greater portion of total body fluid. In situations of volume depletion, such as vomiting and diarrhea, this body fluid imbalance results in abnormalities of water and electrolyte metabolism. Therefore, careful monitoring of fluid and electrolytes is critical for postoperative care.

Daily fluctuations are regulated by feedback mechanisms between the hypothalamic osmoreceptors and volume receptors in the aortic arch, the cardiac atrium, the posterior pituitary, and the collecting ducts of the kidney. Plasma osmolality is maintained between 285 and 295 mOsm/kg. During hemorrhage or dehydration, in which there is a decrease in extracellular volume, ADH is released and causes water retention at the level of the renal collecting ducts. These homeostatic responses result in a return of plasma osmolality to normal.

Both term and premature infants experience an appreciable loss of body weight over the first days of life.[11] This change appears to be due largely to loss of extracellular water, which undergoes a sharp decline in the immediate postnatal period.[12] In addition, sodium, which is mainly in the extracellular space, is lost in amounts exceeding intake during the first week of life. This negative sodium balance continues to occur even after sodium containing feedings are instituted. It is not necessary to replace sodium and chloride losses that occur during the first week of life, because these losses appear to accompany a physiologic reduction of extracellular water. A reasonable goal in judging requirements of water and electrolytes in the newborn appears to be the prevention of clinical and chemical dehydration but not necessarily achieving a zero balance (intake = output) of water, sodium, and chloride.[13]

CALORIC MAINTENANCE

Body composition and metabolic rate change with growth and postnatal age. Infants and children have proportionally higher water content, a higher metabolic rate, and a greater body surface per unit of weight than adults. Calories, water, and electrolytes are required by infants and children for both maintenance of body metabolism and growth. Premature infants have a high water content due to their relatively large extracellular compartment and low fat reserves.[12] In addition,

Table 3-5 Recommended Ranges of Electrolyte Supplementation (mEq/kg/24 hr) for Pediatric and Adolescent Patients Receiving Total Parenteral Nutrition

Electrolyte	Infant (<10 kg)	Pediatric (10-30 kg)	Adolescent (>30 kg)
Calcium	0.5-3.0	5-20	10-15
Magnesium	0.5-1.0	4-24	8-24
Potassium	2-4	20-240	90-240
Sodium	2-4	20-150	60-150
Acetate	2-8	20-120	80-120
Chloride	4-12	20-150	60-150
Phosphorus	0.5-1.0	6-50	30-50

Adapted from Teitelbaum DH, Coran AG. Perioperative nutritional support in pediatrics. *Nutrition*. 1998;14:130-142.

their glycogen stores are comparatively small. As a result, they have limited caloric reserve and are therefore more susceptible to metabolic disturbances caused by stress.[1]

Caloric requirements in infants are represented in Table 3-1.[1] The minimal caloric requirement for a newborn, derived from oxygen consumption studies, is approximately 34 kcal/kg/24 hr. This requirement doubles over the first 9 weeks of life and then returns to approximately 24 kcal/kg/24 hr in older children and adults.

The energy expenditure of infants and children can be estimated from the body weight (Table 3-2). These estimates are based on basal metabolic expenditure plus an average increment for activity in bed, which is higher per kilogram body weight in younger children than in older ones. Extra caloric requirements (above basal) are caused by excess metabolic stress, including increased muscular activity, thermal stress, and excessive loss of body fluids. For example, fever can raise caloric expenditure by 25% to 75%. Table 3-3[14] demonstrates the kilocalorie and protein maintenance requirements in infants and children. These values may substantially increase during times of metabolic stress.

FLUID AND ELECTROLYTE MAINTENANCE

Fluid balance is a critical aspect of the care of postoperative patients. Maintenance water and electrolyte requirements in children vary with weight and size (Tables 3-4[14] and 3-5[14]). With this variation taken into consideration, formulas can be derived that estimate basic fluid requirements (Table 3-6[15]). From these formulas, one can calculate the volume of maintenance fluid needed based on weight. Children are best monitored for dehydration by monitoring urine output. As a measure of meeting fluid requirements, urine output in children should be maintained at 1 to 2 mL/kg/hr.[15] Stress, fever, and increased activity all increase the demand.

The definition of adequate fluid maintenance is the replacement of urine output plus insensible losses, minus the water produced by routine metabolism (Table 3-7[1]). Specific fluid requirements are difficult to quantify because of the kidney's ability to adjust renal losses according to intake.[16] Urine output (measurable losses) should account for approximately 50% of the calculated maintenance fluid.[9] Insensible losses occur by water evaporation through the skin and lungs. Because they have a greater surface area, children have a higher percentage of water loss (25 to 45 mL/kg/24 hr) than do adults (15 to 20 mL/kg/24 hr). Children on mechanical ventilation, like adults, have negligible respiratory loss because of humidification. Water that is produced by metabolism is related to caloric use. However, this amount is negligible in normal situations and is usually not factored into the calculation of maintenance needs. Abnormal losses such as vomiting, diarrhea, stomal secretions, nasogastric tube contents, and third-space losses should be tracked meticulously and need to be replaced volume for volume. The electrolyte composition of these losses should be taken into consideration and the electrolytes replaced accordingly.[15]

Resuscitation fluids are divided into colloid and crystalloid. A larger volume of crystalloid than colloid is required to produce an equal expansion of the ECF. The composition of maintenance fluid is shown in Table 3-8. Typical crystalloid solutions are normal saline, which is isotonic to plasma, and

Table 3-6 Maintenance Fluid Requirement Formulas in Children

Body Weight	Requirement* (mL/kg/hr)	Requirement* (mL/kg/day)
First 10 kg	4	100
Second 10 kg	2	50
Each additional kg	1	25

*Add amounts obtained for each portion of the child's weight to obtain the total requirement.

Adapted from Filston HC, Edwards CH III, Chitwood WR Jr, et al. Estimation of postoperative fluid requirements in infants and children. *Ann Surg*. 1982;196:76.

Table 3-7 Sources of Water Loss in Children

Source	Loss (mL/kg/24 hr)
Insensible water loss	21-30
Pulmonary	7-10
Dermal	14-20
Urine	25-62
Stool	2
Total	48-94

Adapted from Hensle TW. *Metabolic Care of the Neonate and Infant with Urologic Abnormalities: Clinical Pediatric Urology*. Philadelphia: WB Saunders; 1985.

Table 3-8 **Composition of Maintenance Fluids**

Intravenous Solution	Na (mEq/L)	Cl (mEq/L)	Glucose (g/L)	Osmolality (mOsm/kg)
Ringer lactate	130	109	*	272
D5 0.9% normal saline	154	154	50	308
D5 0.45% normal saline	77	77	50	154
D5 0.25% normal saline	33	33	50	75

Ringer lactate, which mimics the electrolyte composition of plasma and is also isotonic. Dextrose 5% is added to the solution to protect erythrocytes and to provide energy for the brain. Fluid and electrolyte requirements for the postoperative patient can be calculated from the body weight and the appropriate solution administered.

Hypovolemia

Hypovolemia in infants and children is often caused by diarrhea but can be the result of any other process that does not allow the net intake to match losses. The degree of hypovolemia can often be gauged from the history, physical examination, and supplementary laboratory data. Weight loss, tachycardia, hypotension, dry mucous membranes, a lack of tears, a sunken fontanelle, and decreased skin turgor are all clinical signs of moderate to severe dehydration. A urine specific gravity greater than 1.0020, an increased hematocrit, and an increased blood urea nitrogen level are also suggestive of significant dehydration. In patients with mild dehydration (5% body weight loss), these clinical findings are often not present and laboratory studies are not indicated. However, if any of these signs are present, electrolyte abnormalities and acid-base disturbances should be evaluated by laboratory testing.[9]

Replacement of mild dehydration (<5% body weight loss) can often be managed by oral rehydration therapy, even in patients with diarrhea and vomiting.[17] Two types of oral replacement fluids are used; oral maintenance solutions and oral rehydrational solutions. Maintenance fluids are commonly used along with parenteral rehydration to supplement losses from common problems such as gastroenteritis. Rehydrational fluids have a higher sodium concentration and are typically given in small doses (50 mL/kg) over 4 hours in mild dehydration.[9] Once rehydration is accomplished, maintenance fluids are then introduced.

In patients with moderate to severe hypovolemia (>5% body weight loss), which can exist perioperatively due to a loss of intravascular volume, the goal is to rapidly expand the extracellular volume, prevent shock, and improve renal perfusion. Replacement is initially given in boluses of normal saline or Ringer lactate. The urine output is then monitored as a measurement of the patient's improved intravascular volume. As mentioned previously, an adequate urine output in children is considered to be between 1 and 2 mL/kg/hr.[15] As the replacement fluid is given, the urine output is monitored closely. These fluid boluses rapidly expand the intravascular volume and then equilibrate with the rest of the extracellular space. An estimation of the overall deficit can be made using the knowledge that 10% dehydration correlates with a loss of approximately 100 mL/kg.[9] Typically, half the deficit is replaced over the first 8 hours, and the second half is given over the next 19 hours. The replacement of sodium losses is calculated to be 8 to 10 mEq/kg/day plus the maintenance amount.[9]

Serial measurements of weight, clinical signs of dehydration, and urine output should all be made at regular intervals. The electrolyte and acid-base status of blood should also be checked routinely to allow proper adjustment of electrolyte concentrations in replacement fluids. Metabolic acidosis, which is often seen with hypovolemia, usually resolves once fluid and electrolyte balance and renal function are restored. In severe situations, it may be necessary to add bicarbonate to restore the pH balance sooner. In difficult situations in which it is hard to distinguish between hypovolemia, renal failure, cardiac failure, and sepsis, central venous pressure lines and pulmonary wedge catheters can be used to help clarify the situation. Once the patient is isovolemic, as determined by adequate urine output, hypotonic maintenance fluids are used, in addition to replacement fluid with measured abnormal losses as needed.[15]

Sodium Abnormalities

Sodium is the major cation of the ECF. Fluctuations in the serum sodium concentration can cause major fluid shifts and metabolic abnormalies.[10]

Hyponatremia

Hyponatremia is one of the most frequent electrolyte abnormalities that occur in hospitalized patients. Symptoms associated with hyponatremia include nausea, anorexia, vomiting, apathy, muscle aches, headache, and weakness.[18] Severe hyponatremia can cause irritability, confusion, seizures, and coma. In the perioperative period, ADH is secreted in response to intravascular depletion, which leads to the development of hyponatremia. In addition, intravascular depletion leads to a decreased GFR, which limits the kidney's ability to excrete free water, causing hyponatremia. Hyponatremia causes the overall osmolality to decrease, and water moves along the osmotic gradient into cells, swelling them. If this deficit is replaced too rapidly, brain cells are put at risk of dehydration and damage resulting in central pontine myolysis. For this reason, hyponatremia needs to be corrected slowly, at a rate no faster than 10 to 20 mEq/day.[9] Correction of the underlying problem is imperative in the treatment of hyponatremia.

Hypervolemic hyponatremia is seen most often in conditions such as congestive heart failure, renal failure, and liver disease, in which water is retained along with sodium, leading to significant clinical manifestations, including peripheral and pulmonary edema. Treatment involves sodium and water restriction. In patients with renal failure, dialysis may be needed to remove the excess fluid and correct the sodium deficit.[9]

Situations of *isovolemic hyponatremia* are most often caused by the syndrome of inappropriate antidiuretic hormone (SIADH), which leads to excessive water reabsorption. The most frequent underlying causes of inappropriate ADH production are tumors, drugs, and central nervous system disorders. Isovolemic hyponatremia is also occasionally seen when extremely dilute feedings are given. Treatment includes water and sodium restriction with the addition of diuretics in severe situations.[9]

Hypovolemic hyponatremia most often results from volume depletion, including gastroenteritis, fasting, or third-space losses (e.g., ascites, burns, peritonitis, extensive surgery). In these situations, the kidney attempts to compensate by retaining sodium, which leaves the urine sodium dilute. Hypovolemic hyponatremia can also be the result of renal sodium and water losses. This occurs in salt-wasting nephropathies, renal tubular acidosis, excess diuretic use, and situations of renal resistance to mineralocorticoids. In all of these conditions, the urine sodium is rather concentrated. Treatment of hypovolemic hyponatremia necessitates volume expansion with normal saline or lactated Ringer solution. Again, it is important to correct the sodium deficit slowly (<10 mEq/day). In situations of symptomatic hyponatremia (lethargy and disorientation), diuretics are used in conjunction with normal saline solution to prevent cerebral dehydration, seizures, and coma. When such situations occur, hypertonic saline solution (3%) may be used to raise the sodium concentration, but not by more than 1 to 2 mEq/hr or halfway to normal within an 8-hour period.[9]

Hypernatremia

Symptoms associated with hypernatremia include confusion, lethargy, muscle twitching, hyperreflexia, and convulsions.[18] Patients with hypernatremia are typically dehydrated, with more water being lost than sodium. Hypernatremia can be the result of excessive peripheral losses or diabetes insipidus. It can also occur with the ingestion of such drugs as lithium, cyclophosphamide, and cisplatin. Premature infants are predisposed to hypernatremia because of their inability to properly regulate water and sodium levels. The risk of hypernatremia is that it can cause cerebral dehydration, which can in turn lead to tearing of arachnoid tissues and intracerebral bleeds.[9]

Hypervolemic hypernatremia is usually attributed to the excess secretion of aldosterone, which causes increased sodium reabsorption and potassium loss. Treatment of hyperaldosteronism includes the use of diuretics along with administration of hypotonic fluids.[9]

Isovolemic hypernatremia may be the result of diabetes insipidus (central or peripheral) or excessive insensible losses. Diabetes insipidus results in the collecting tubule's becoming impermeable to water. This can be caused by a defect in central ADH release or by inability of the kidney receptors to respond to ADH. Treatment includes correction of the sodium concentration through the administration of hypotonic saline solution. If central diabetes insipidus is the cause, exogenous ADH can correct the imbalance.[9]

Hypovolemic hypernatremia occurs when water losses are greater than sodium losses. This can result from diarrhea, vomiting, or diabetes insipidus. Treatment should begin with the administration of normal saline or lactated Ringer solution to restore the plasma volume. The elevated sodium level should be lowered slowly, by no more than 10 mEq/day, to prevent cerebral edema and fatal complications.[9]

Potassium Abnormalities

Potassium is the major intracellular cation; it is present in low concentration in the ECF. It is this concentration gradient between the ECF and the intracellular fluid that allows muscular, cardiac, and neuronal tissues to function appropriately. Therefore, potassium abnormalities can be life-threatening.[10]

Hypokalemia

Symptoms of hypokalemia include arrhythmias, neuromuscular excitability, hyporeflexia, decreased peristalsis, and rhabdomyolysis. Hypokalemia (defined as a serum potassium level <3 mEq/dL) is most often the result of excessive renal and gastrointestinal losses. Renal causes include both diuretic and mineralocorticoid use, as well as renal tubular diseases such as Bartter syndrome.[9] Gastrointestinal causes include excessive vomiting or nasogastric suctioning.

Cardiac arrhythmias, respiratory distress, and muscle weakness require immediate replacement with KCl intravenously. This is typically done in boluses of 10 mEq in 100 mL normal saline solution over a 1-hour period; once serum levels are repleted, the therapy may be changed to oral replacement. KCl is typically used in patients with metabolic acidosis, whereas citrate or bicarbonate preparations are more often employed in cases of renal tubular acidosis.[9,19] Patients with renal tubular diseases such as Bartter syndrome require KCl replacement, potassium-sparing diuretics, and prostaglandin synthase inhibitors.

Hyperkalemia

Symptoms of hyperkalemia can include cardiac arrhythmias, paresthesias, muscle weakness, and paralysis. Hyperkalemia (defined as a serum potassium level >5.5 mEq/dL) is most often the result of a hemolyzed blood specimen with liberation of high concentrations of potassium or a specimen drawn above the potassium-containing fluid line. If such causes are suspected, another specimen should be drawn. True causes of hyperkalemia include transcellular shifts, as seen in metabolic acidosis and tissue catabolism. Chronic or acute renal failure and hypoaldosteronism can cause serum potassium levels to be increased. Chronic use of nonsteroidal anti-inflammatory drugs or diuretics may also cause hyperkalemia.[9]

Patients with hyperkalemia require cardiac monitoring during treatment. Calcium gluconate may be given intravenously to stabilize the myocardium, with each dose lasting approximately 30 minutes. Glucose with insulin or $NaHCO_3$ may also be given intravenously to drive potassium into the intracellular space. To remove potassium from the body, ion exchange resins such as Kayexalate may be used, either orally or as enemas. These bind potassium to the resin in the gastrointestinal tract, which is then excreted. In situations of severe hyperkalemia or unstable cardiac status, hemodialysis may be employed to remove potassium quickly.

Hypocalcemia

Calcium is mostly concentrated within the bone matrix; only 0.1% of body calcium is in the ECF. Calcium exists in three forms: 40% is protein bound, 10% is complexed to phosphate and other anions, and 50% is ionized. Metabolic acidosis decreases protein binding, primarily to albumin, and increases ionized calcium; metabolic alkalosis has the opposite affect. Hypocalcemia is the reduction of the ionized portion. Clinical hypocalcemia manifests with perioral paresthesias, carpal pedal spasm, tetany, and generalized seizure. Neuromuscular manifestations include Chvostek sign, which is twitching of the corner of the mouth produced by tapping over the facial nerve, and Trousseau sign, which is spasm of the fingers produced by inflating a blood pressure cuff above systolic pressure. Electrocardiographic changes include prolonged QT and ST intervals and peaked T waves.

Perioperative hypocalcemia may be the result of hypomagnesemia, acute renal failure, septic shock, rhabdomyolysis, or acute pancreatitis. However, these conditions rarely produce symptoms. Only clinically symptomatic hypocalcemia needs to be treated with calcium supplementation.

Hypomagnesemia

Hypomagnesemia occurs from dietary deficiency, excessive alcohol consumption, and chronic diuretic use. Persistent hypomagnesemia can cause hypocalcemia and contributes to the persistence of hypokalemia by causing renal potassium wasting. Magnesium should be replaced, either orally or intravenously, to the upper-normal plasma range, especially in the setting of hypokalemia and hypocalcemia.

ACID-BASE DISTURBANCES

Normal physiologic pH is between 7.35 and 7.45. A normal pH depends on both renal and pulmonary functions. To evaluate acid-base disturbance in any patient, an arterial blood gas analysis along with a serum electrolyte panel must be obtained.[20] Disturbances in this equilibrium can be the result of changes in acid production, buffering, or excretion, any of which can lead to metabolic acidosis or alkalosis. An increase or decrease in the respiratory expulsion of CO_2 can lead to a respiratory acidosis or alkalosis.[10]

Metabolic Acidosis

Symptoms of acidosis include cardiac arrhythmias, hypotension, and pulmonary edema. Metabolic acidosis results from the addition of acid or removal of base from the plasma. The respiratory system attempts to compensate for this imbalance by blowing off carbon dioxide (CO_2) to correct the body pH. Acids in plasma are buffered in large part by bicarbonate (HCO_3^-) and other unmeasurable anions such as proteins, phosphates, sulfates, and organic bases.[9,20] These unmeasurable bases make up the anion gap. The normal anion gap is 10 to 12 mEq/L.[10] The anion gap may be calculated from the plasma concentrations of certain ions, by the formula

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

Non–Anion Gap (Hyperchloremic) Acidosis

Non–anion gap acidosis occurs in situations in which HCO_3^- is lost from the kidney or the gastrointestinal tract or both. When this occurs, Cl^- (along with Na^+) is reabsorbed to replace the HCO_3^-; this leads to the hyperchloremia, which leaves the anion gap in normal range.[10]

Diarrhea causes a hyperchloremic, hypokalemic metabolic acidosis. Treatment depends on the severity of the acidosis incurred. In mild to moderate acidosis (pH >7.2), fluid and electrolyte replacement is often all that is required. Once adequate renal perfusion is restored, excess H^+ can be excreted efficiently, restoring the pH to normal. In severe acidosis (pH <7.2), the addition of intravenous bicarbonate may be needed to correct the metabolic deficit. Before bicarbonate is administered, a serum potassium level should be obtained. The addition of bicarbonate can worsen hypokalemia, leading to neuromuscular complications. Hyperchloremic acidosis also occurs with renal insufficiency and renal tubular acidosis.[9,20]

Anion Gap Acidosis

Causes of anion gap acidosis include lactic acidosis, diabetic ketoacidosis, the ingestion of poisons, and renal failure. Lactic acidosis is often seen in the setting of sepsis and hypovolemia; it may also be caused by inborn errors of metabolism. Treatment hinges on correcting the underlying problem. With sepsis and hypovolemia, antibiotics and fluid resuscitation may be all that is required. In more severe situations, the administration of bicarbonate may temporarily stabilize the pH while systemic treatment takes effect.

Diabetic ketoacidosis is the result of anaerobic metabolism of glucose to β-hydroxybutyrate and acetoacetate. Treatment requires volume resuscitation and the administration of insulin, which helps metabolize ketoacids. Most situations do not necessitate the use of bicarbonate.

Poisoning with salicylates or ethylene glycol leads to ketosis and lactic acidosis with the compensatory loss of HCO_3^-. These conditions are best corrected by removing the drug via gastric lavage, charcoal, or, in severe situations, dialysis.[9,20]

Metabolic Alkalosis

Symptoms of metabolic alkalosis include central nervous system changes, muscular irritability, cardiac arrhythmias, and seizures. Lethargy and confusion are often also seen when the body decreases the breathing rate in order to retain CO_2. Metabolic alkalosis occurs as a result of losing acid or gaining base. Causes include alkali ingestion, vomiting, nasogastric tube losses, and hyperaldosteronism.

In mild alkalosis, chloride replacement is needed to allow the renal excretion of bicarbonate. In severe alkalosis, hydrochloride or ammonium chloride may be given to correct the balance. If the alkalosis was caused by vomiting, potassium may also need to be supplemented along with chloride. If the underlying alkalosis was caused by hyperaldosteronism, the antagonist spironolactone is given to correct the situation.[9,20]

Respiratory Acidosis

Respiratory acidosis is caused by an increase in the partial pressure of carbon dioxide, P_{CO_2} (decrease in respiration), which drives down the body pH. Causes include airway obstruction, central nervous system depression, immaturity, and neuromuscular problems. Treatment is aimed at correcting the underlying problem, and bicarbonate usually is not given.[9,20]

Respiratory Alkalosis

Respiratory alkalosis is caused by a decrease in P_{CO_2} (increase in respiration), which drives up the pH. Alkalosis is most frequently caused by hyperventilation, which is often the result of central nervous system disorders or psychological disease. Dizziness and confusion are the symptoms usually seen and are thought to be the result of a decreased cerebral blood flow. In situations of acute hyperventilation, the patient can rebreathe into a bag to drive the CO_2 level up and thus decrease the respiratory rate. The main treatment for respiratory alkalosis is correction of the underlying problem.[9,20]

NUTRITIONAL CONSIDERATIONS

Developing children have a high metabolic rate and low body stores of fat and nutrients. This makes them more susceptible to metabolic disturbances in the perioperative period. Prolonged fasting, stress, and trauma lead to a depletion of body stores, primarily protein, which decreases immunocompetence and increases morbidity and mortality.[21] Several issues must be taken into consideration when developing a plan for nutritional support in children: (1) the nutritional status (nutritional assessment), (2) the metabolic status (total urinary nitrogen), (3) the individual protein and calorie requirements, (4) the goal of nutritional therapy, (5) the presence of a functioning gastrointestinal tract, (9) appetite, and (7) the presence of specific organ dysfunction.

The biochemical marker used to evaluate nutritional status is albumin. Hypoalbuminemia may be caused by hepatic dysfunction, protein loss from the vascular compartment, altered hydration status, or undernourishment. Hypoalbuminemia has been correlated with increased morbidity and mortality in hospitalized children.[22] The protein needs of neonates and infants are much larger than those of children or adults due to their needs for growth and maintenance of body weight[14] (see Table 3-3). A negative nitrogen balance occurs for the first 3 days postoperatively. Infants undergoing major surgery benefit from nitrogen administration.[23]

Three types of support exist to meet the needs of children with nutritional depletion[24-26]: enteral alimentation, isotonic intravenous therapy (partial parenteral nutrition), and hypertonic intravenous therapy (total parenteral nutrition, or TPN).

Enteral Alimentation

Enteral alimentation is the preferred method of nutrition in patients with an intact gastrointestinal tract. Enteral feedings have been demonstrated to stimulate the immune system and to preserve gastrointestinal function better than parenteral feedings.[27,28] Enteral feeding preserves normal intestinal villus and microvillus structure, which may prevent the development of bacterial translocation from the intestine and septicemia.[29] Additionally, it is much cheaper than parenteral nutrition. Most infants and children tolerate oral supplementation, but feeding tubes are necessary in some cases.

Many commercially prepared liquid diets are available (Table 3-9).[21] These typically provide between 35 and 45 kcal/kg/day, with a calorie-to-nitrogen ratio of about 300:1. High-nitrogen formulas have a calorie-to-nitrogen ratio of about 150:1. The particular carbohydrate, fat, and protein contents of these commercially prepared diets vary widely, and specific formulations are used for specific patients' needs.

Problems of nausea, vomiting, and diarrhea can be overcome by the use of smaller Silastic feeding tubes and by incrementally increasing the feeding rate slowly over time. Typically, infusion rates begin at 10 mL/hr and may be increased to a maximum of 90 mL/hr. A minimal infusion rate of 20 mL/hr is needed for gut preservation and immune stimulation.

Great success has been achieved with enteral alimentation in support of the nondepleted, noncachectic patient.[30] However, the enteral route is not always adequate to deliver enough nourishment rapidly and efficiently in the malnourished patient. In addition, malnutrition can lead to anatomic changes in the gastrointestinal tract that can exacerbate malabsorption. A more aggressive approach to nutritional restoration in the depleted patient is often warranted because of time constraints or the degree of nutritional depletion.

Isotonic Parenteral Nutrition

Isotonic parenteral nutrition (also called partial parenteral nutrition or protein-sparing therapy) involves the delivery of isotonic amino acids via a peripheral vein in a 3% or 3.5% solution with appropriate vitamin, mineral, and electrolyte additives. The solution must have an osmolarity of less than 600 mOsm to be tolerated by peripheral veins. This form of therapy depends on the mobilization of endogenous fat stores for fuel and the provision of peripheral amino acids for obligate protein needs. The ideal protein requirement to maintain nitrogen balance is between 1.5 and 2 g/kg/day. Amino acid infusions provide a means by which lean body mass can be maintained in a starved state, but they are not a substitute for TPN. Isotonic parenteral nutrition minimizes catabolism as opposed to providing the fuel necessary for anabolism. In the well-nourished patient who faces a prolonged period of inpatient starvation, amino acid infusions provide a more sustainable approach to body mass preservation than do hypocaloric carbohydrate feedings.[31]

Table 3-9 **Enteral Nutrition Formulas**

Product	Calories/mL	Protein (g/L)	Fat (g/L)	Carbohydrate (g/L)	kcal/N Ratio
Osmolite HN	1.06	44	37	141	150:1
Osmolite	1.06	37	39	145	178:1
Ensure	1.06	37	37	145	178:1
Vitaneed	1.0	40	40	128	156:1
Nutren Fiber	1.0	40	38	127	156:1
Peptamen	1.0	40	39	127	156:1
Vivonex T.E.N.	1.0	38	3	206	175:1
Ensure Plus	1.5	55	53	200	170:1
TraumaCal	1.5	83	68	142	116:1
Pulmocare	1.5	63	92	106	150:1
Isocal HCN	2.0	75	102	200	170:1
Suplena	2.0	30	96	255	427:1
Amin-Aid	2.0	19.4	46	366	830:1
PediaSure	1.0	30	50	110	209:1

Adapted from Hensle TW, Kennedy WA. An update on nutrition in the surgical patient. AUA Update Series. Linthicum, MD: American Urological Association Education and Research, Inc; 1995; Vol. XIV:Lesson 3.

Table 3-10 **Composition of Standard Hyperalimentation Solution (per 2618 mL)**

Component	Amount
Amino acids	100 g
Dextrose	200 g
Fat	100 g
Sodium	150 mEq
Potassium	82 mEq
Calcium	9 mEq
Magnesium	10 mEq
Chloride	150 mEq
Acetate	187 mEq
Zinc	3.5 mg
Copper	1.4 mg
Manganese	0.35 mg
Chromium	14 μg
Multivitamin 12	10 ml
Phosphorus	15 mM

Adapted from Hensle TW, Kennedy WA. An update on nutrition in the surgical patient. AUA Update Series. Linthicum, MD: American Urological Association Education and Research, Inc; 1995; Vol. XIV:Lesson 3.

Hypertonic Intravenous Nutrition

Once a state of nutritional depletion is reached and the infant or child is unable to tolerate oral intake, the vehicle to rebuild body mass and achieve anabolism is TPN. Prolonged starvation is the main impetus for starting TPN. Older children and adults can undergo starvation for up to 10 days before TPN is initiated. However, term infants can only go 4 to 5 days, and preterm infants only 1 to 2 days, without nutrition before TPN is started.[14] Another indication is gastrointestinal dysfunction, including chronic malabsorption, diarrhea, bowel obstruction, and enterocutaneous fistulas.

Hypertonic solutions are composed of 20% to 25% dextrose and 4.25% amino acids, with adequate amounts of vitamins, micronutrients, and cofactors. Standard TPN solutions contain approximately 1000 kcal/L and 9 to 7 g of nitrogen per liter and exert 2000 mOsm of pressure at the point of delivery. Essential fatty acids are provided to the patient in the form of continuous infusion of a 3% lipid solution. Standard formulations have been developed (Table 3-10).[24] Glutamine, an amino acid, has been implicated in mucosal preservation by decreasing bacterial translocation during sepsis and stress while also helping to prevent the decrease of secretory immunoglobulin A seen frequently with parenteral nutrition.[32]

Because of the extreme hypertonicity of hyperalimentation, it must be delivered through a central venous line, and its rate must be rigidly controlled. The central venous line is placed and maintained with strict sterile technique. In patients who require longer courses of TPN, a subcutaneous tunneled line (Broviac, Groshong, or Hickman catheter) may be employed to minimize infection. A Millipore filter is usually placed in the line, and the line is used for no other purposes and is changed frequently to prevent contamination.[33,34] Hyperalimentation solutions should be administered initially at low rates of infusion until tolerance has been achieved, after which the rate may be gradually increased to the desired caloric need.[35]

Complications associated with TPN can be classified as technical, septic, or metabolic. Technical complications relate mainly to the placement of the central venous line. Pneumothorax, hydrothorax, brachial plexus injuries, arterial or venous injuries, and air emboli have all been reported. Septic complications related to the catheter or solution have been reported in 2% to 3% of cases, even when strict hygiene is employed.[36] The most common metabolic complications reported are those related to glucose metabolism and resulting hypoglycemia or hyperglycemia. The most dangerous is the hyperosmolar nonketotic coma, which results from unchecked hyperglycemia, glycosuria, and a massive osmotic diuresis. The resultant cerebral dehydration can lead to coma and death. These sequelae can be easily and safely controlled by the addition of insulin to the TPN solution. Other metabolic complications such as hypophosphatemia, hypercalcemia, hypocalcemia, and hypomagnesemia are often caused by the amount of the relevant substances delivered and are easily and safely corrected. Deficiencies in essential fatty acids and trace elements have also been seen in long-term TPN use. The routine administration of commercial fat sources and the addition of trace elements can alleviate these problems. Elevation of liver enzymes is also seen in the long-term use of TPN. This is thought to be caused largely by the delivery of calories in excess of the patient's need, which leads to an increased insulin response resulting in hepatic lipogenesis and enzyme derangements.[24,37]

REFERENCES

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SECTION 2

MORPHOLOGIC INVESTIGATIONS

CHAPTER 4

PRENATAL DIAGNOSIS OF FETAL RENAL ABNORMALITIES

Lyn S. Chitty and S. M. Whitten

Renal abnormalities account for approximately 17% of all anomalies diagnosed prenatally.[1] Many of the severe bilateral abnormalities manifest in the second trimester, often by the time of the routine fetal anomaly scan at about 20 weeks, but many are not detected until late in the second or into the third trimester of pregnancy (Table 4-1).[2-6] Although the prognosis in severe cases that are associated with oligohydramnios or anhydramnios is often clear, the widespread establishment of routine prenatal ultrasonography for fetal anomaly screening means that we are increasingly detecting abnormalities that are clinically silent at birth and of uncertain pathologic significance. Pediatricians are now frequently faced with management dilemmas as to how to investigate and treat neonates with prenatally diagnosed renal abnormalities. Theoretically, the routine offer of prenatal diagnosis should decrease postnatal morbidity from renal disease, because early detection allows for rapid initiation of treatment in the postnatal period. However, no study has yet conclusively demonstrated this effect in the majority of cases.[7] Uncertainty regarding the natural history of many prenatally diagnosed abnormalities requires long-term follow-up studies to be undertaken so that postnatal, and indeed prenatal, intervention can be appropriately planned.

It is important to remember that prenatal ultrasonography can describe only anatomic findings. It gives little indication as to function in most cases and cannot be used to make a histopathologic diagnosis. A definitive diagnosis, particularly in families with no relevant past history of renal abnormality, must often await the results of postnatal investigations. The ideal approach to the prenatal diagnosis of renal abnormalities is for the fetal medicine specialists to work in close collaboration with the pediatric urologists and nephrologists; if possible, they should see patients in a combined clinic with both specialties present. In some cases, input from genetic studies may be appropriate, because there is a high incidence of renal abnormalities in genetically inherited syndromes. In all cases in which the pregnancy ends in a perinatal death or termination of pregnancy, detailed postnatal pathologic examination should be encouraged, with expert histology and collection of tissue for DNA analysis, so that the diagnosis can be accurately defined. This allows for counseling of parents with regard to recurrence risks and for appropriate management in future pregnancies, when early prenatal diagnosis using molecular genetic techniques may be feasible.

In this chapter, we attempt to define renal abnormalities using an anatomic classification based on how they manifest prenatally, with details of specific conditions within each category and broad management options where available.

ASSOCIATION OF RENAL ABNORMALITIES WITH ANEUPLOIDY

It should be remembered that the spectrum of renal disease seen in the prenatal period is very different from that seen postnatally, and in many cases there is an association with aneuploidy. Even in the absence of another risk factor, many studies have shown an increased incidence of aneuploidy among fetuses with upper tract dilatation.[8,9] This should be borne in mind when counseling parents, particularly if additional risk factors, such as older maternal age or positive Down syndrome screening, are present. In these cases, karyotyping should always be discussed. The karyotypic anomalies most commonly present in association with structural renal abnormalities are trisomy 18, trisomy 13, 45X, triploidy, trisomy 9 mosaic,[10] 10q duplication, and 18q deletion. There is a wide range of associated extrarenal anomalies, including cardiac anomalies, spina bifida, exomphalos, diaphragmatic hernia, limb anomalies, and structural brain abnormalities such as holoprosencephaly. There is also an association with genetic syndromes, and the heart, spine, and forearms should be carefully examined in all cases to exclude conditions such as VATER syndrome. Specific genetic syndromes are considered later in the chapter (Table 4-2).

SONOGRAPHY OF THE NORMAL RENAL TRACT

Assessment of the fetal renal tract depends on the ascertainment of normal anatomy followed by the exclusion of abnormal pathologic findings. In the United Kingdom, most women are offered an initial ultrasound scan in the first trimester, usually between 11 and 14 weeks of gestation, followed by a detailed anomaly scan between 18 and 21 weeks. If no abnormality is detected, this may be the last routine scan during pregnancy. However, many women do have additional scans during the third trimester for indications such as placental site localization, assessment of presentation, and assessment of fetal growth and well-being. The opportunity to assess the fetal kidneys may also be taken at this time.

The fetal kidneys migrate from their pelvic origin to the renal fossae during the 6th to 9th week of gestation. They can be imaged from about 9 weeks' gestation by transvaginal ultrasound (TVUS), and approximately 80% are identified by 11 to 12 weeks' gestation.[11,12] With transabdominal ultrasound, kidneys can be visualized from 12 to 13 weeks' gestation, but they are more usually seen from approximately 14 weeks onward. In early pregnancy, the kidneys appear uniformly

Table 4-1 Gestational Age (Weeks) at Diagnosis of Renal Abnormality

	Obstructive Uropathy			Renal Agenesis			Bilateral Dysplasia		
Study, Year, and Ref. No.	**<24**	**>24**	**ND**	**<24**	**>24**	**ND**	**<24**	**>24**	**ND**
Levi et al, 1995[2]	9	56	18	6	8	5	11	7	3
Levi et al, 1992[3]	2	32	13	3	3	0	4	5	2
Chitty et al, 1991[4]	7	0	0	4	0	0	2	1	0
Crane et al, 1994[5]	10	16	1	1	0	0	2	1	0
Smith et al, 1999[6]	—	—	—	21	30	14	—	—	—
Total (%)	28 (17)	104 (63)	32 (20)	35 (37)	41 (43)	19 (20)	19 (50)	14 (37)	5 (13)

ND, not detected.

Table 4-2 When to Consider Karyotyping

- Always consider background aneuploidy risk
- Has there been previous aneuploidy screening?
- Bilateral mild renal pelvis dilatation + other markers
- Upper tract dilatation
- Bilateral multicystic dysplastic kidneys
- Echogenic kidneys
- Dilated bladder
- Any renal abnormality in the presence of extrarenal structural abnormality
- If oligohydramnios precludes detailed fetal anatomic examination
- Aneuploidy is rare in the following:
  - Isolated duplex kidney
  - Isolated pelvic kidney
  - Isolated unilateral multicystic kidney

Table 4-3 Key Points for Assessment of the Fetal Renal Tract

- Are there two kidneys?
- Are they normally positioned in the renal fossae?
- Are they of a normal size?
- Is the echogenicity normal?
- Is the renal pelvis present and of a normal size and appearance?
- Can you see the ureters? (Ureters should not normally be seen.)
- Can you see the bladder?
- Does the bladder fill and empty during a 20-minute scan?
- Is there any bladder abnormality (e.g., keyhole, thickened wall, ureterocele)?
- Is the amniotic fluid volume normal?

echogenic. With increasing gestation, corticomedullary differentiation takes place, and by 18 to 22 weeks, the renal pelvis and calyceal pattern can be identified. Fetal kidneys continue to grow throughout pregnancy, and several charts of fetal renal size are available.[13] Measurements have been made in both longitudinal and cross-sectional planes using both TVUS in early pregnancy[14] and transabdominal ultrasound from 12 weeks onward.[13]

The fetal bladder can be identified from 11 to 12 weeks' postmenstrual age, and persistent absence of the bladder should be considered as abnormal from approximately 15 weeks' gestation onward.[11,12] Normal fetal ureters are not visualized with ultrasound. Fetal urine production begins at 10 weeks' gestation, although tubular function does not begin until about 14 weeks. Before that time, the amniotic fluid is thought to be primarily a dialysate of fetal blood across the skin, which is permeable. By the middle of the second trimester, the fetal kidneys account for most of the amniotic fluid production; any impairment in production will be manifested as oligohydramnios, and assessment of volume will provide some reflection of overall renal function. An adequate amount of amniotic fluid is required to allow development of the fetal lungs and to enable movement of the fetus within the amniotic cavity. Oligohydramnios may be caused by mechanical urinary flow impairment, pathologic renal impairment (e.g., bilateral renal agenesis), or poor renal perfusion due to placental insufficiency. Subjective ultrasound evaluation of amniotic fluid volume around the fetus is approximate, whereas objective assessment may be made by measuring the amniotic fluid index.

Fetal gender can be determined by ultrasound from 12 weeks' gestation. In earlier pregnancy, differentiation between a male and a female can be difficult because of the prominence of the genital tubercle.[15] Gender can be determined from 6 weeks' gestation by analysis of cell-free fetal DNA circulating in the maternal blood.[16]

PRINCIPLES OF ASSESSING FETAL RENAL ABNORMALITIES

The visualization of two kidneys, the bladder, and the amniotic fluid volume are the mainstays of assessment of fetal renal anatomy. The presence of abnormality may be an isolated finding, but often it is associated with other renal tract anomalies or with extrarenal abnormalities. Prognosis often depends on such additional findings, so the identification of an abnormality in one part of the fetal renal tract should prompt a detailed assessment of the rest of the renal tract, followed by evaluation of the rest of the fetal anatomy and an overall assessment of other risk factors for aneuploidy or an underlying genetic abnormality (Table 4-3).

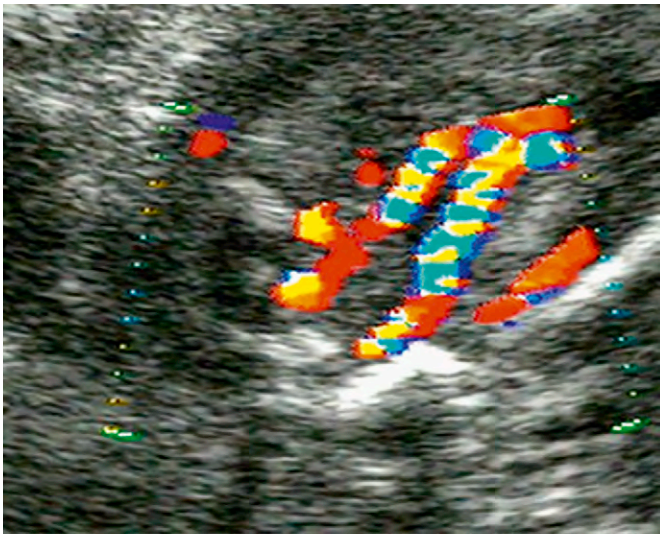

Figure 4-1 Color Doppler ultrasound image showing the paravesical vessels outlining an empty bladder in bilateral renal agenesis.

ABSENT AND ABNORMALLY SITED KIDNEYS

Failure to visualize one or both kidneys may occur if there is renal agenesis or if the kidney is sited ectopically. A search should be undertaken to establish how many kidneys are present, where they are sited, whether they appear anatomically normal, whether there are any extrarenal abnormalities, and whether the amniotic fluid volume is normal.

Renal Agenesis

Renal agenesis occurs when there is complete absence of one or both kidneys. The underlying pathology is not certain but probably involves failure of early development of the ureteric bud. Agenesis may also result as an end stage of dysplastic change and regression of a multicystic kidney; this can occasionally occur early in gestation, before the first scan, so a definitive determination of the cause may not always be possible prenatally.

Unilateral agenesis is thought to occur in approximately 1 of every 1400 births. If it is an isolated condition, there is usually a normal volume of amniotic fluid, and the contralateral kidney becomes enlarged through compensatory hypertrophy. Overall prognosis is good if the finding is isolated; however, unilateral renal agenesis may also be associated with extrarenal abnormalities, particularly of the spine and heart. In males, unilateral renal agenesis is frequently associated with dysplasia of the testis, which must be therefore excluded by ultrasonography after birth.[17] In the postnatal period, renal ultrasound scans should be performed to confirm the prenatal diagnosis and to examine the contralateral kidney, because there is a significant incidence of reflux and other abnormalities. Neonates should also be carefully examined for other subtle abnormalities, such as hemivertebrae, which may not have been detected prenatally and which may be seen in the VATER or VACTERL spectra (discussed later).[18]

The incidence of bilateral renal agenesis is approximately 1 in 4000,[19] with a male-to-female ratio of 2.5:1. Classically, the findings include failure to identify either kidney, a persistently absent bladder, and oligohydramnios. Visualization of the fetus can be difficult, but the use of color Doppler ultrasonography can enhance the diagnosis, because failure to demonstrate renal artery flow is evident even in the presence of severe oligohydramnios (Fig. 4-1).[20] The sonographic diagnosis of bilateral renal agenesis is complicated because, in the absence of the kidneys, the adrenal glands may take on a globoid or reniform shape and often occupy the renal fossae. Bilateral renal agenesis is lethal and holds a recurrence risk of 2% to 3%. There is an association with other anomalies, aneuploidy, and genetic syndromes, and a detailed assessment of the fetus should be undertaken. Termination of pregnancy should be discussed, and the importance of postmortem examination stressed. Both parents should be scanned, because there is some evidence for an inherited basis, which may affect the recurrence risk in individual cases.

Ectopic (Pelvic) Kidney

An ectopic kidney occurs as a result of failure of normal migration of the kidneys during early embryologic development along the cranial-caudal axis. Most commonly, the kidney is located in a pelvic position, although iliac, abdominal, and thoracic locations have been reported.[21,22] The incidence of simple renal ectopia based on postmortem data varies between 1 in 500 and 1 in 1200.[23-25] There is an equal sex incidence and a slight preponderance to the left side; 10% of cases are bilateral.[26] The ectopic renal mass is often smaller than expected and has an unusual shape because of the presence of fetal lobulations. The vascular supply is usually anomalous and depends on the final position of the kidney.

During the routine second-trimester scan, an empty renal fossa should raise the suspicion of an ectopic kidney and initiate a search within the pelvis (Fig. 4-2). The diagnosis is not always easy to make; the adrenal gland may be mistaken for a hypoplastic kidney, or bowel in the renal bed for a cystic renal mass. The diagnosis can usually be made with the use of transabdominal ultrasound,[27] but it may sometimes be necessary to perform TVUS to fully assess a kidney positioned deep within the pelvis. Pelvic kidneys are often smaller than expected for the gestational age, and they may have an abnormal shape as a result of malrotation.[28] Color Doppler assessment may be a useful aid to diagnosis and will demonstrate the blood supply to the ectopic kidney, which may arise from the lower aorta or from the common iliac, middle sacral, or inferior mesenteric vessel.[28] Both kidneys should be assessed for size, echogenicity, and renal pelvis dilatation (RPD); the bladder and external genitalia should be examined for associated urogenital anomalies; and a detailed examination of the fetus should be carried out to search for associated extrarenal anomalies. Coexisting urogenital abnormalities occur in 15% to 45% of these cases, including contralateral renal anomalies such as agenesis or upper tract dilatation; hypospadias, cryptorchidism, and urethral duplication in males; and uterine and vaginal anomalies in females.[29,30] Extrarenal anomalies in the cardiovascular, skeletal, and gastrointestinal systems can occasionally be found in association with ectopic kidneys,[26] which have also been described in association with a number of genetic syndromes, including Beckwith-Wiedemann syndrome (BWS), branchio-oto-renal dysplasia, and abnormalities in chromosomes 19 and 22.

There are limited data regarding the long-term implications of a prenatal diagnosis of pelvic kidney. In two series, prenatally diagnosed pelvic kidneys were found mainly in isolation and without obvious significant consequence.[27,28] Masnata and colleagues[31] reported on 32 cases, 15 of which were accurately diagnosed before birth. Surgery was required for four children with a contralateral anomaly, and four underwent nephrectomy for a large pelvic multicystic dysplastic kidney. Overall renal function was normal in all of these cases. In a study of 12 pelvic kidneys seen in our unit, all either were

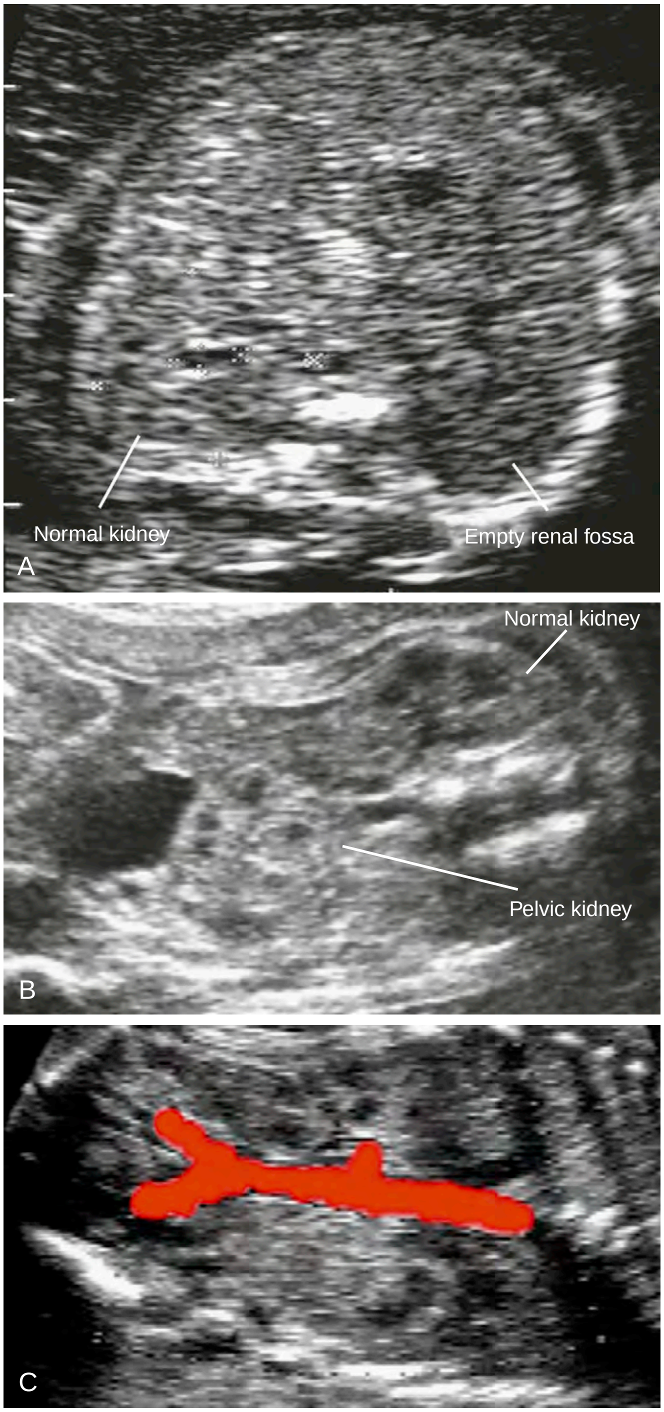

Figure 4-2 Sonographic images showing a normal kidney with an empty renal fossa **(A),** a pelvic kidney located anterior and inferior to the normal kidney **(B),** and an absence of normal renal artery flow to the pelvic kidney **(C)**. The pelvic kidney in **C** was subsequently identified as arising from the iliac vessels.

small at initial diagnosis or decreased in size during pregnancy. Amniotic fluid volume remained within the normal range, although it approached the 5th percentile in one case later in pregnancy. The contralateral kidney appeared normal during pregnancy in seven cases, and in five cases there was compensatory hypertrophy. The remaining five cases had contralateral renal anomalies. Overall postnatal renal function, as determined either by uptake and drainage of radioactive isotope and differential renal function on technetium 99m dimercaptosuccinic acid (DMSA) or mercaptoacetyltriglycerine (MAG3) scanning or by measurement of the glomerular filtration rate (GFR), remained normal in 10 cases; in these cases, at least one kidney (pelvic or other) had an otherwise normal appearance.[32]

Therefore, currently available data suggests that the presence of a unilateral pelvic kidney is not inherently associated with a poor outcome. Where the pelvic kidney involutes or is dysplastic, a normal contralateral kidney is associated with a good outcome. Where the pelvic kidney has an otherwise normal appearance, pathology in the contralateral kidney often governs treatment. In the presence of bilateral renal pathology, a poor outcome may be anticipated to the same extent as for normally sited bilateral dysplastic kidneys. In this situation, the option of termination of pregnancy should be discussed. The natural history toward involution of the pelvic kidney also suggests that a proportion of individuals with a unilateral kidney diagnosed in childhood or adulthood may well have originally had an ectopic kidney.

ABNORMAL SIZE AND ECHOGENICITY OF THE KIDNEYS

Normally, the fetal kidneys are of similar size and with uniform echogenicity, similar to that of the fetal liver. However, alterations in renal size and appearance of the cortex can present a difficult diagnostic dilemma,[33] particularly in the presence of a normal liquor volume, because the underlying etiologies are diverse.[34] Large "bright," or hyperechogenic, kidneys are occasionally seen at the time of a routine ultrasound scan or later in pregnancy when a woman is scanned for another clinical indication (Fig. 4-3). Defining the underlying pathology may not be straightforward, and it is essential to conduct a detailed scan of the fetus for other renal and extrarenal tract pathology. If the bladder is enlarged, with or without dilated ureters, then the findings may reflect an obstructive uropathy. If the kidneys and all measurements lie above the 95th percentile, then an overgrowth syndrome (e.g., BWS, Perlman syndrome, Simpson-Golabi-Behmel syndromes)[33] could be considered (Fig. 4-4). If diagnosis of a syndrome can be made, then the prognosis will be that associated with the syndrome. Review by a geneticist at this stage may be helpful. Karyotyping should be discussed, particularly if other malformations are detected, because this can be a feature of trisomy 13. Consultation within a combined renal clinic, with input from pediatric nephrologists and urologists together with the geneticist, is essential. Long-term follow-up studies are urgently needed for this group of fetuses to better inform prenatal counseling (Table 4-4).

Isolated Hyperechogenic Kidneys

If, after detailed scanning and karyotyping, it appears that the fetus has isolated hyperechogenic kidneys and a normal karyotype with no evidence of renal tract obstruction, the differential diagnosis comprises renal dysplasia, autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD), nephrocalcinosis, or (rarely) a variant of normal. A detailed family history and ultrasound examination of the parents' kidneys may help in identifying the underlying cause, particularly in ADPKD, because most carriers have renal cysts by their late twenties.

Accurate prognosis can be difficult, although liquor volume is a key indicator. Reduced or absent liquor indicates that the outcome is likely to be poor; such pregnancies

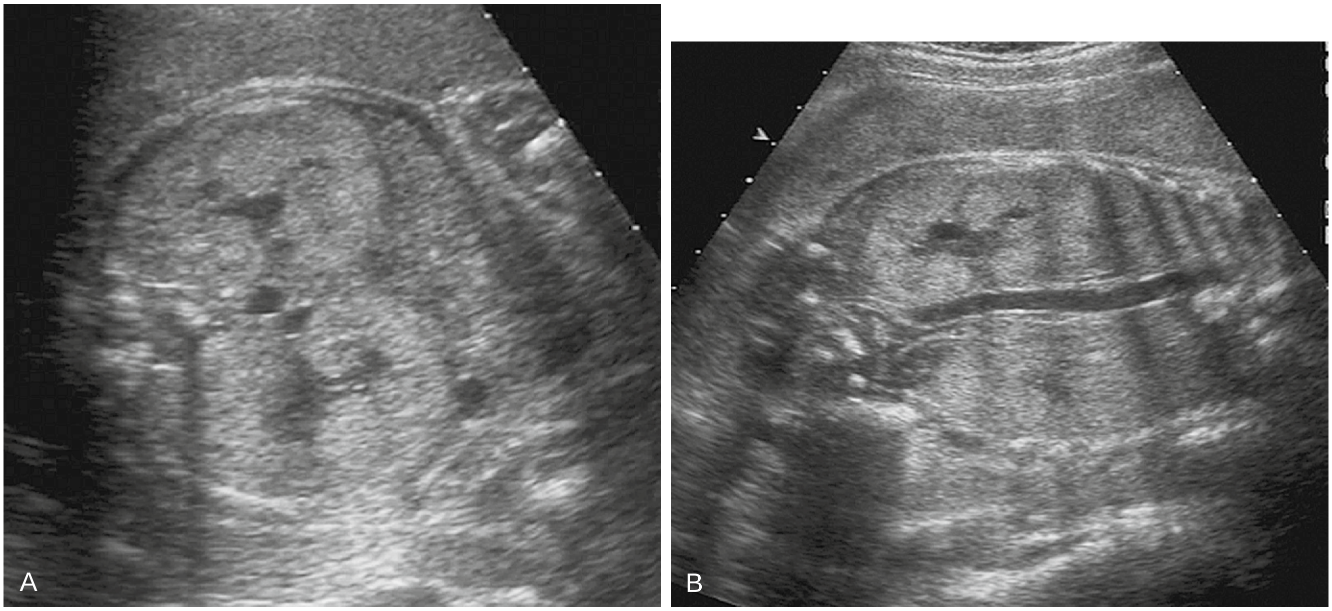

Figure 4-3 Enlarged echogenic kidneys seen in the axial **(A)** and coronal **(B)** planes with associated absence of amniotic fluid. After birth, the cause was identified histologically as autosomal recessive polycystic kidney disease.

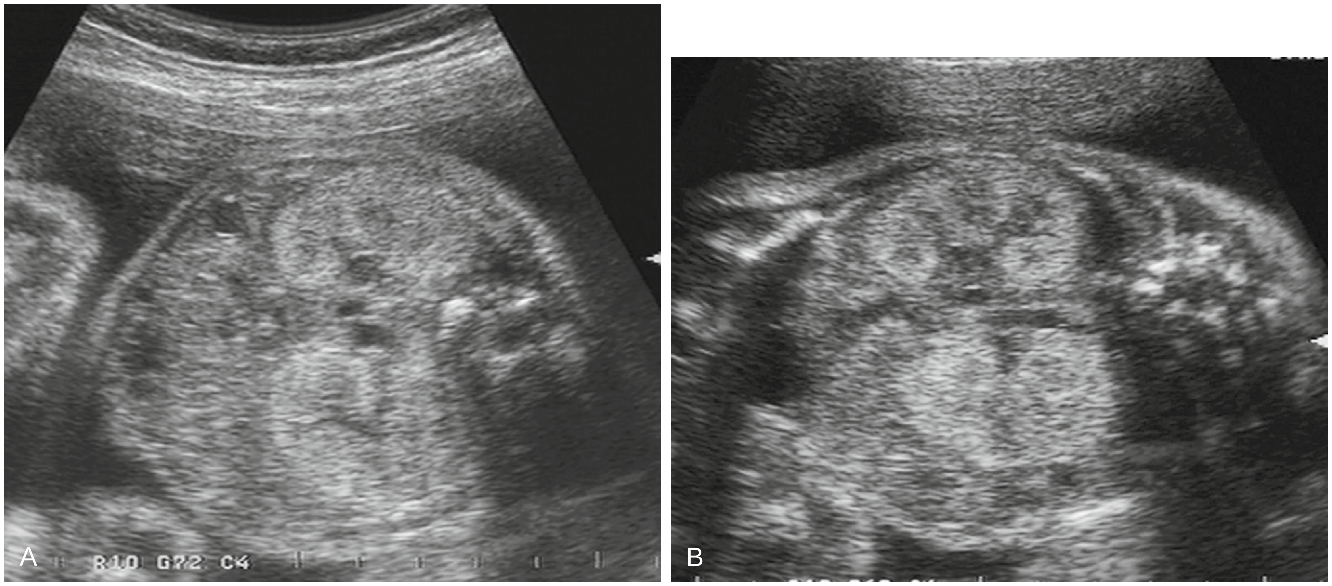

Figure 4-4 Enlarged echogenic kidneys seen in the axial **(A)** and coronal **(B)** planes in a fetus with Beckwith-Wiedemann syndrome. Note the presence of normal liquor in this case.

frequently end in a neonatal death subsequent to pulmonary hypoplasia as well as renal failure. In these circumstances, termination of pregnancy is a reasonable option, if the condition is detected before viability, and parents should be strongly encouraged to consent to postmortem examination, because the histologic findings will be critical in defining the underlying pathology. Tissue should be stored for DNA extraction; increasingly, the genetic etiology is known, and an early prenatal test using molecular techniques may be possible in future pregnancies.

In the presence of normal liquor volume, serial scanning should be undertaken to monitor the size of the kidneys and renal function as indicated by liquor volume. Unless there is a positive family history, definition of the etiology usually must await the results of postnatal investigations.

Dysplastic Kidneys

Renal dysplasia is a histologic diagnosis, but the diagnosis may be inferred prenatally from increased echogenicity of the renal cortex, which results from the lack of normal renal parenchyma and structurally abnormal kidneys. Dysplastic kidneys can be any size, ranging from massive kidneys distended with multiple large cysts up to 9 cm in diameter, commonly termed multicystic dysplastic kidneys (MCDK), to normal-sized or small kidneys with or without cysts. Dysplasia can be unilateral or bilateral, and MCDK is one of the most common causes of abdominal masses in the newborn. The incidence of unilateral MCDK is between 1 in 3000 and 1 in 5000 births, compared to 1 in 10,000 for bilateral dysplasia.[35]

MCDK confined to one kidney is often an incidental finding, but bilateral dysplasia should lead to consideration of

Table 4-4 Key Points for Assessment of Hyperechogenic Kidneys

- Examine the whole renal tract
- Measure the kidneys
- Measure the amniotic fluid volume
- Search for extrarenal abnormalities
- Consider karyotyping
- Ascertain the family history
- Scan the parental kidneys
- Refer to a multidisciplinary clinic for counseling by pediatric nephrologists and geneticists
- Arrange for detailed postmortem examination by an expert perinatal pathologist in the event of termination, intrauterine demise, or neonatal demise

aneuploidy or inherited conditions. There is a strong association between dysplasia and obstruction: MCDKs are classically attached to atretic ureters; renal dysplasia frequently develops in conjunction with lower urinary tract malformations that impair urine flow; and many features of dysplasia can be generated in animals by experimental obstruction of the urinary tract during development.[36,37] Therefore, the lower urinary tract should be carefully assessed in all cases of presumed renal dysplasia.

Sonographic Findings

The classic presentation of MCDK is a multiloculated abdominal mass consisting of multiple thin-walled cysts which do not appear to connect (Fig. 4-5). The cysts are distributed randomly; the kidney is usually enlarged with an irregular outline, and no renal pelvis can be demonstrated. Circumferential cysts may occasionally be detected in kidneys of more normal size, particularly in association with lower urinary tract obstruction. Parenchymal tissue between the cysts is often hyperechogenic. In the unilateral form liquor volume is usually normal, but oligohydramnios or anhydramnios is likely to be present with bilateral MCDK. Differential diagnosis of multicystic dysplasia includes upper tract dilatation and other intra-abdominal cystic masses. Color Doppler ultrasonography may be useful in determining the diagnosis, because the renal artery is always small or absent in MCDK, and the Doppler waveform, when present, is markedly abnormal, with a reduced systolic peak and absent diastolic flow. The appearance of MCDKs may change during pregnancy; frequently there is an initial increase in size, often surpassing normal expected growth, followed by decrease in size as gestation progresses. Dysplastic kidneys may even disappear completely, either before or after birth,[38-40] suggesting that many patients diagnosed with renal agenesis may have originally had dysplasia.

Bilateral severe dysplasia without associated cystic change may be difficult to distinguish from renal agenesis, especially because detailed examination of the fetal anatomy is difficult in the presence of oligohydramnios or anhydramnios. *Unilateral small dysplastic kidneys* are much more difficult to detect in utero, unless they are specifically sought after diagnosis of other abnormalities in the urinary tract or other organ systems (Fig. 4-6). The bladder is usually normal in unilateral dysplasia unless there is lower tract pathology; in bilateral disease, the bladder may be difficult to detect, and color flow Doppler may be useful, as in bilateral renal agenesis (see Fig. 4-1).

Further Prenatal Investigation of Dysplastic Kidneys

Detection of dysplastic kidneys should stimulate a detailed examination of the fetus for other structural abnormalities, including heart, spine, extremities, face, and umbilical cord, because up to 35% of these fetuses have extrarenal anomalies. These are more likely to occur in fetuses with bilateral rather than unilateral disease.[40] Chromosome analysis should also be discussed with the parents if extrarenal abnormalities are detected or dysplasia is bilateral. In isolated unilateral renal dysplasia, risks of chromosomal defects are low. In a study of 102 fetuses with MCDK, 10 (9.8%) had an abnormal karyotype, but in all cases extrarenal anomalies were present.[40]

Detailed examination of the other kidney is essential in unilateral presentations, because 30% to 50% of kidneys contralateral to dysplastic kidneys are either structurally abnormal (duplex system, pelviureteric obstruction, agenesis, or ectopic) or affected by vesicoureteral reflux (VUR),[40-42] and bilateral abnormalities have a major impact on long-term prognosis. It is also worth considering renal ultrasonography of parents and siblings, because numerous kindreds have been described with autosomal dominant inheritance of aplasia, dysplasia, and other urinary tract abnormalities including VUR, duplications, and horseshoe kidneys.[43,44] The exact familial incidence of renal/urinary tract disease is unknown, although one large study looking at index cases of bilateral agenesis/severe dysplasia reported that 9% of relatives had renal malformations[45]—most commonly unilateral, often clinically silent, renal agenesis. Relatives should also be questioned directly about a history of diabetes, not only because maternal diabetes is a significant risk factor for recurrence in subsequent pregnancies, but also because some families may have undiagnosed “renal cysts and diabetes” syndrome (discussed later). Recurrence risks are small (2% to 3%), unless the renal dysplasia is associated with a genetically inherited syndrome.

Prognosis of Dysplastic Kidneys

The prognosis for isolated dysplastic kidneys is critically dependent on whether there is bilateral or unilateral disease. *Bilateral dysplasia* has a very poor outlook, particularly if there is significantly reduced liquor volume and the kidneys either fail to grow or reduce in size during gestation. Infants with severe bilateral disease often die in the neonatal period, secondary to a combination of pulmonary hypoplasia and renal failure. Less severe bilateral dysplasia may be compatible with life. Affected infants should be referred to the regional pediatric nephrology center so that further investigations and management can be instigated as soon as possible, but there should also be a low threshold for immediate prophylactic antibiotic therapy to prevent urinary tract infections, which could potentially exacerbate the renal problems. The likelihood of developing chronic renal failure in fetuses with bilateral dysplasia is difficult to predict before birth, but several studies have correlated postnatal renal function with outcome and suggested that a calculated GFR of less than 15 mL/min/1.73 m^2 at 6 months, or 25 mL/min/1.73 m^2 at 18 months of age is associated with a worse prognosis.[46,47]

Fetuses with *unilateral renal dysplasia* have a much better prognosis, especially in the presence of a “normal” contralateral kidney. The majority of dysplastic kidneys involute[38,39] without causing any problems, and this is associated with compensatory hypertrophy of the contralateral kidney, either

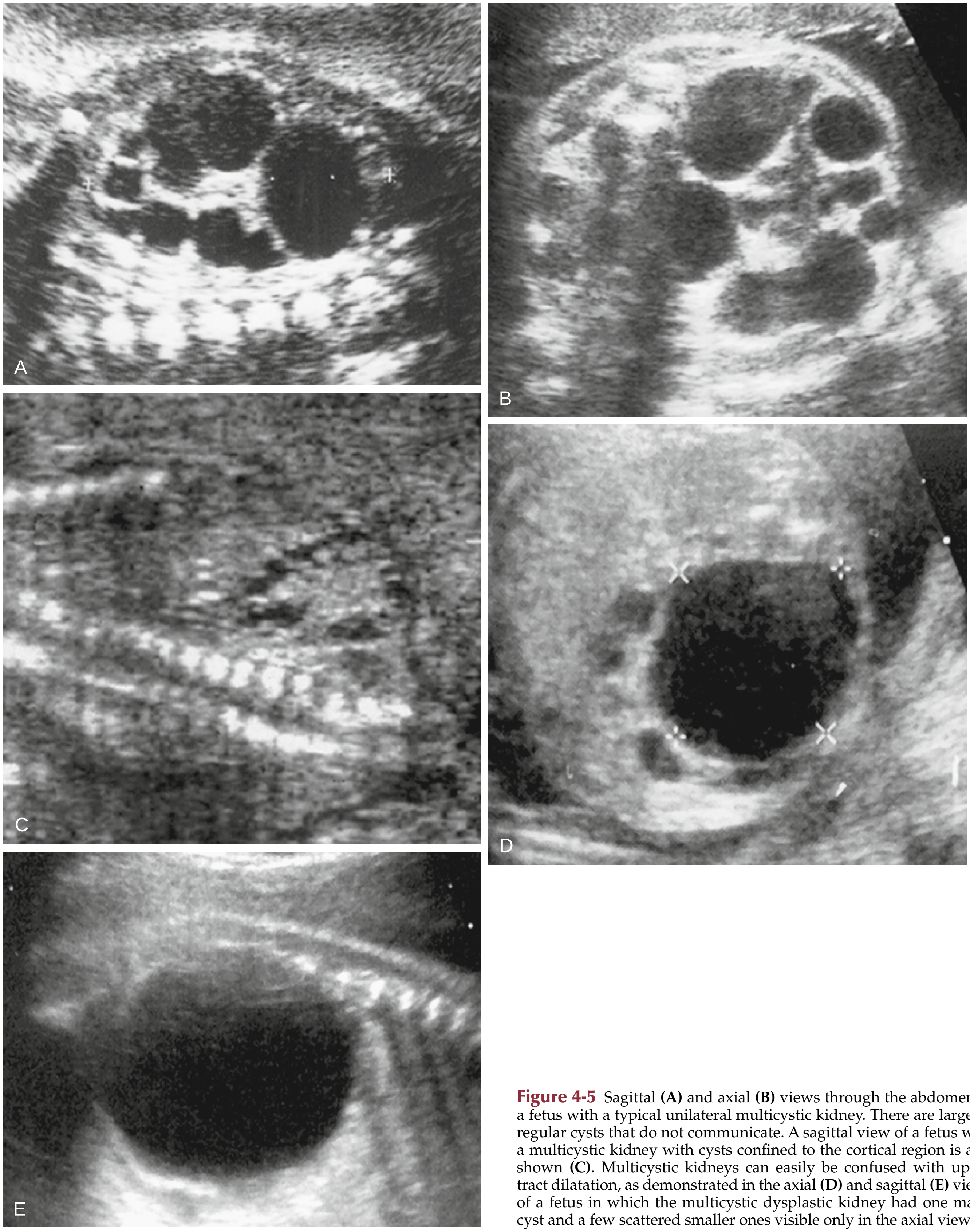

Figure 4-5 Sagittal **(A)** and axial **(B)** views through the abdomen of a fetus with a typical unilateral multicystic kidney. There are large irregular cysts that do not communicate. A sagittal view of a fetus with a multicystic kidney with cysts confined to the cortical region is also shown **(C)**. Multicystic kidneys can easily be confused with upper tract dilatation, as demonstrated in the axial **(D)** and sagittal **(E)** views of a fetus in which the multicystic dysplastic kidney had one major cyst and a few scattered smaller ones visible only in the axial view.

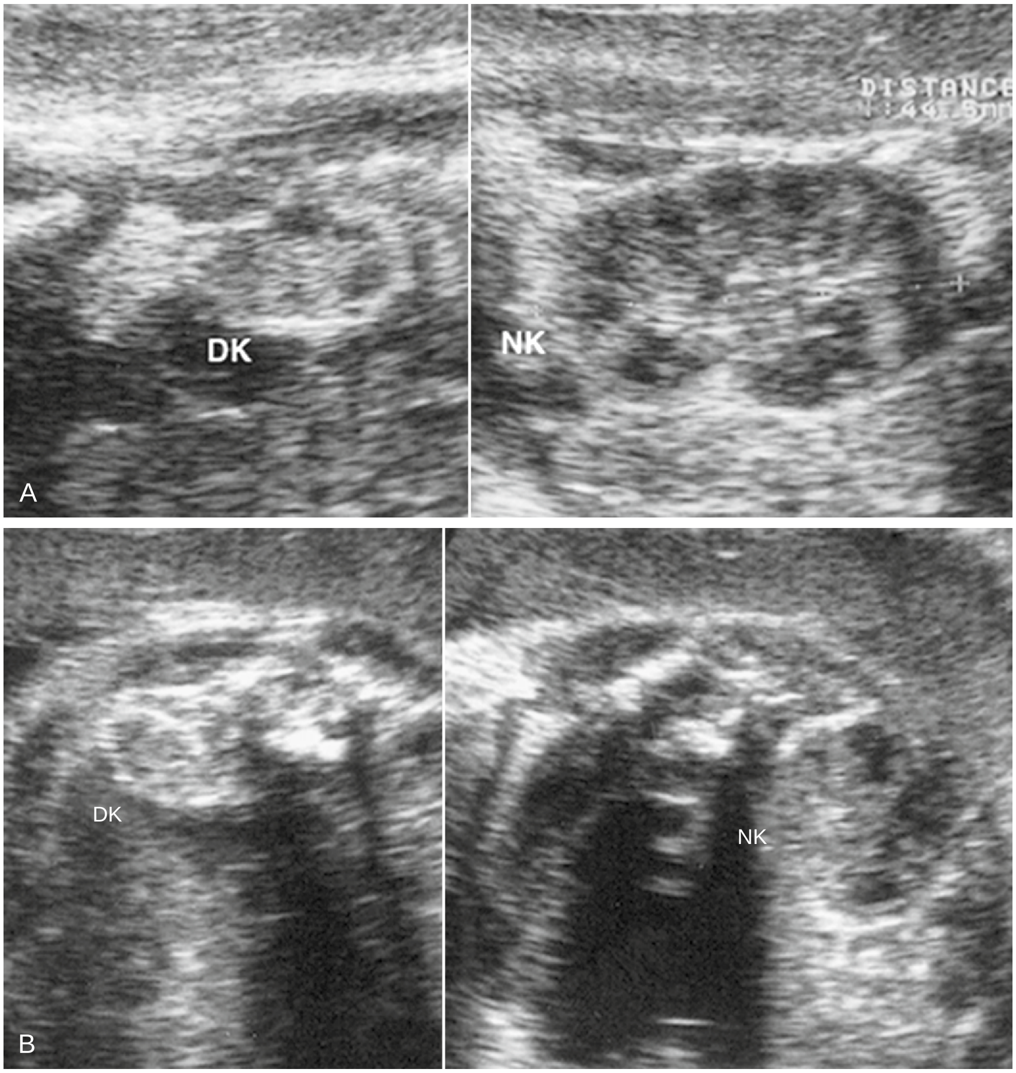

Figure 4-6 Sagittal **(A)** and axial **(B)** views of a unilateral small dysplastic kidney (DK) with the normal contralateral kidney (NK) showing compensatory hypertrophy.

before birth or postnatally.[48] Numerous studies have shown that the risk for associated abnormalities is between 30% and 50%, with the most common being contralateral malformations such as VUR or obstructed megaureter and hypoplasia.[48]

Polycystic Kidney Disease

Polycystic kidney disease can be divided into dominantly and recessively inherited forms (formerly known as adult and infantile forms, incorrectly suggesting a clear classification in terms of age at onset of disease). Both forms can manifest in the prenatal period, although definitive diagnosis relies on specific mutation analysis that may not be possible prenatally unless specific linkage analysis has already been performed in a family at known high risk.

Autosomal Recessive Polycystic Kidney Disease

The typical in utero presentation of ARPKD is enlarged, hyperechogenic kidneys with loss of corticomedullary differentiation, presumably due to the numerous small cysts that are undetectable by ultrasound, and oligohydramnios (see Fig. 4-3). It may also be difficult to differentiate the calyceal pattern in some cases. Increased echogenicity of the kidneys has been demonstrated as early as 12 to 16 weeks,[49,50] but kidney size may be normal at that time. There is usually evidence of renal enlargement and increased echogenicity by 24 weeks of gestation, although occasionally the diagnosis cannot be made until the third trimester or postnatally.[51] Onset of oligohydramnios may also be gradual, with progressive worsening of liquor volume from the second trimester.

Because the gene location for ARPKD is known, although not the gene, molecular diagnosis after chorionic villus sampling can be used for prenatal diagnosis in families at high risk where genetic studies performed before pregnancy are informative.[52,53] Magnetic resonance imaging has also been used to diagnose ARPKD in utero, but this technique is not in regular use in most centers and could not be used for families with no prior history.

PROGNOSIS FOR PRENATALLY DIAGNOSED ARPKD

The prognosis for patients with prenatally diagnosed ARPKD is either very poor, with death in the neonatal period, or quite reasonable if they survive into infancy. Early onset of ultrasonically detectable renal changes and oligohydramnios is associated with poor prognosis. Neonates usually die from respiratory failure rather than renal problems, although aggressive ventilatory support and emergency nephrectomy may improve the outcome.[54] Genetically, the severe cases map to the same region as the milder forms, and therefore they cannot be distinguished by currently available molecular genetic techniques.[55] Survivors beyond the neonatal period have a much better prognosis[56,57] than that reported in most textbooks (progressive renal and hepatic failure, with death during childhood in most cases). The 1-year survival probability after the first month was reported as 94% for male patients and 82% for female patients in a large study of more than 100 children,[56] and actuarial renal survival rates of 86% at 1 year and 67% at 15 years was described by another group.[57] Aside from declining renal function, the major problems reported were urinary tract infections, severe systemic hypertension requiring multiple-drug therapy, and hepatic fibrosis with portal hypertension leading to hypersplenism and gastroesophageal varices.

Autosomal Dominant Polycystic Kidney Disease

ADPKD is more common than ARPKD, with approximately 1 in every 1000 people carrying the affected gene.[58] It rarely manifests prenatally or in early childhood.[59] It is classically a late-onset disease manifesting with hypertension, renal cysts, and renal failure in the fourth or fifth decade of life.[60] If ADPKD does develop prenatally in a family, there is increased likelihood that further affected children will also present early.[61]

SONOGRAPHIC FINDINGS

The sonographic presentation of ADPKD is usually as large, hyperechogenic kidneys; in contrast to ARPKD, individual cysts may also be detected.[62] The size of the cysts in ADPKD is variable, and a mixture of small and large cysts can be observed. Liquor volume is usually preserved. Definitive diagnosis may be possible prenatally if a family history of ADPKD can be established or if one parent is found to have renal cysts on ultrasound, because new mutations occur in fewer than 10% of cases, and almost all affected individuals have at least one cyst by the age of 30 years.[63] In families at known prior risk who request it, prenatal diagnosis is best done by molecular analysis of chorionic villi if linkage has been established before pregnancy. It is particularly important to establish the diagnosis of ADPKD if it has been inherited from the mother, because hypertensive mothers with ADPKD have a high risk for fetal and maternal complications and require close monitoring to prevent the development of preeclampsia.[64] In one case, the appearances were reported to change during pregnancy, with large bright kidneys seen at 21, 23, and 34 weeks of gestation but normal-sized kidneys and corticomedullary differentiation after birth.[65] ADPKD was confirmed in that infant when cysts developed at 11 months of age in one kidney and at 20 months in the other.

PROGNOSIS FOR PRENATALLY DIAGNOSED ADPKD

MacDermot and colleagues analyzed patients presenting with ADPKD in utero or during the first few months of life (excluding those where parents elected to terminate the pregnancy) and reported that 43% died before 1 year of age, with the most useful prognostic indicators being the presence of oligohydramnios and the outcome of pregnancy of a previously affected sibling.[66] This estimate of mortality appears likely to be exaggerated, however, because it is based on historical data that are biased toward the worst cases, such as those with oligohydramnios, which is relatively rare although clearly linked to poor prognosis. In contrast, Fick and colleagues reported on 11 children with ADPKD diagnosed in utero ($n = 6$) or during the first year of life ($n = 5$); the only death occurred from termination of pregnancy at 27 weeks' gestation.[67] Hypertension, often requiring multiple-drug therapy, developed in nine of these children, and end-stage renal failure in two. It was suggested that risk factors for early-onset disease were an affected mother, an affected sibling, or an apparent prenatal new mutation. The same group reported the results of 312 children with ADPKD who were monitored for up to 15 years.[68] GFR decreased only in two children with unusually severe, early-onset disease, and, once again, the only major problem was control of blood pressure. Taken together, these studies suggest that the prognosis for prenatally diagnosed ADPKD is good unless oligohydramnios is present.

Other Genetic Syndromes Associated with Abnormal Kidneys

Many renal abnormalities occur as an isolated finding, but the prognosis may be altered considerably by detection of other anomalies that could indicate a genetic disorder or syndrome.[69,70] Although for many genetic conditions specific mutation analysis is now available, this usually requires prepregnancy investigations. In some cases, moreover, the definitive diagnosis may not be suspected until postmortem examination, and by that time it may be too late to establish a cell line to confirm the suspicion by laboratory methods. It is therefore important to take tissue samples prenatally if possible, or at delivery, because postnatal samples may have a high culture failure rate.

Overgrowth Syndromes

The presence of large echogenic kidneys in a fetus with generalized macrosomia and normal or increased liquor points toward the diagnosis of an overgrowth syndrome. All are rare, the most common being BWS and Simpson-Golabi-Behmel syndrome. Prenatally, differentiation among these syndromes can be extremely difficult unless there is a positive family history, a distinctive pattern of structural abnormalities, or a positive molecular or cytogenetic diagnosis. In low-risk cases, distinction usually must await the results of postnatal investigations, and even then there is considerable clinical overlap among the syndromes (Table 4-5).[33,69]

BECKWITH-WIEDEMANN SYNDROME

BWS is characterized by gigantism (which is often, but not always, present at birth), macroglossia, visceromegaly (liver, spleen, kidneys, adrenals), abdominal wall defects (omphalocele and umbilical hernia), and predisposition to embryonal tumors, particularly Wilms' tumor.[71] The features can be extremely variable, and specific dysmorphic features such as ear creases, nevus flammeus, and hemihypertrophy may be useful distinguishing features postnatally.[72] BWS is the result of abnormal expression of imprinted genes involved in growth and cell cycle control lying in the region of chromosome 11p15.[73] It seems that the syndrome is caused by paternal disomy for 11p15.5, which contains the insulin-like growth factor 2 *(IGF2)* gene. In some cases there is a cytogenetic deletion of this region, and in others paternal disomy can be demonstrated; however, in many cases no molecular or cytogenetic abnormality is demonstrable.[72]

Sonographic Findings. Polyhydramnios is often reported in association with bilateral enlarged echogenic kidneys due to BWS (see Fig. 4-4).[33,74] Other features reported include hepatomegaly, macroglossia, generalized macrosomia, and omphalocele. Mild hydronephrosis,[75] placental enlargement,[76] and elevated maternal serum beta-human chorionic gonadotrophin have also been reported.[77] The prognosis for BWS is now recognized to be much better than previously thought,[72]

Table 4-5 Genetic Syndromes Associated with Large Bright Kidneys

Syndrome	Liquor	Renal Cyst	RPD	Macrosomy	Other Abnormalities	Cardiac Abnormalities	Inheritance
ARPKD	N/oligo	–	–	–	–	–	AR
ADPKD	N/oligo	(+)	–	–	–	–	AD
BWS	N/poly	–	±	+	+	–	
Perlman	N/oligo	–	±	+	+	–	AR
SGB	?	?	?	+	+	±	X-linked
Trisomy 13	Oligo	–	±	–	+	±	Sporadic
Meckel-Gruber	Oligo	–	–	–	+	±	AR
Obstructions	N/oligo	–	+	–	–	–	Sporadic
Nephrocalcinosis	N	–	–	–	–	–	
Bardet-Biedel	N/poly	–	–	–	+	–	AR

AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; ARPKD, autosomal recessive polycystic kidney disease; BWS, Beckwith-Wiedemann syndrome; N, normal; oligo, oligohydramnios; poly, polyhydramnios; RPD, renal pelvic dilatation; SGB, Simpson-Golabi-Behmel syndrome.

because developmental problems are associated with either a significant cytogenetic deletion in the region of 11p15.5 or profound hypoglycemia in the neonatal period. The latter can be avoided for all prenatally detected cases by careful neonatal care, so prenatal diagnosis should improve the prognosis for this syndrome. If BWS is suspected, cytogenetic analysis can be performed to exclude the possibility of a deletion on 11p15.5 and uniparental disomy of this region. However, the definitive diagnosis cannot reliably be obtained in this way, because only about 20% of cases have a recognizable abnormality of this region.[72]

SIMPSON-GOLABI-BEHMEL SYNDROME

Simpson-Golabi-Behmel syndrome is an X-linked neonatal overgrowth syndrome that is characterized by a large head with coarse features, hepatosplenomegaly, cryptorchidism, and variable degrees of developmental delay, with some affected individuals having normal intelligence.[78] Associated structural abnormalities amenable to prenatal diagnosis include polydactyly, cardiac abnormalities, vertebral anomalies, and umbilical hernia. Because the condition is X-linked, this diagnosis should be considered only in a male fetus. It has been mapped to Xq25-q27.[79]

Sonographic Findings. The diagnosis should be considered in all cases of large hyperechogenic kidneys in a male fetus with all other measurements lying above the 95th percentile. A finding of polydactyly may be a useful adjunct to diagnosis, as may a diaphragmatic hernia or cardiac anomaly. Referral to a clinical geneticist may be of value, because there is often a family history of X-linked problems, and female carriers may have distinctive facial features.

PERLMAN SYNDROME

Perlman syndrome is a rare, autosomal recessively inherited overgrowth syndrome characterized by general organomegaly, facial dysmorphisms, and renal hamartomas with a tendency to hepatoblastomatosis. Fetal and neonatal mortality rates are high.[74]

Sonographic Findings. The main sonographic features of Perlman syndrome are generalized fetal macrosomia and large echogenic kidneys, secondary to renal hamartomas with or without nephroblastomatosis.[69] Hydronephrosis and hydroureter have been reported, as has a large cisterna magna with skeletal abnormalities.[80] Diaphragmatic hernia and cardiac defects have also been reported.[81] Polyhydramnios is often associated with this syndrome, but oligohydramnios has also been described together with fetal ascites.[69] The prognosis is poor, with neonatal death occurring in many cases, often secondary to pulmonary hypoplasia and prematurity. The survivors have a high incidence of developmental delay and Wilms' tumors.[82]

Non-overgrowth Genetic Syndromes Associated with Renal Abnormality

VATER ASSOCIATION

The VATER spectrum is probably the most common syndromic association with renal anomalies and comprises *v*ertebral anomalies, *a*nal stenosis or atresia, *t*racheo*e*sophageal fistula, *r*adial defects, and renal anomalies. An expansion of this syndrome, known as VACTERL, adds *c*ardiac and nonradial *l*imb defects. The condition is sporadic. The renal abnormalities include agenesis, ectopia, horseshoe kidney, and cysts. The vertebral anomalies are most commonly hemivertebrae that may be seen on ultrasound scanning at 20 weeks. Tracheoesophageal fistula with esophageal atresia can be inferred from the presence of polyhydramnios with or without an absent stomach bubble. Developmental delay is not usually a feature. The presence of renal anomalies, hemivertebrae, and/or radial anomalies with polyhydramnios suggests this diagnosis.[83]

Another association is MURCS (*mü*llerian duct aplasia, *r*enal aplasia, and *c*ervicothoracic *s*omite dysplasia), which, by definition, occurs solely in women, although possible male cases have been reported.[84] It is also thought to be a sporadic disorder.

MECKEL-GRUBER SYNDROME

Meckel-Gruber syndrome is a lethal autosomal recessive syndrome that is characterized by bilateral enlarged echogenic kidneys (100%), encephalocele or other major intracranial abnormality (90%), and postaxial polydactyly (90%).[85] The syndrome has been mapped to chromosome 17q21-24 in Finnish families,[86] and, more recently, a second locus on chromosome 11 has also been identified.[87]

Sonographic Findings. The in utero presentation of Meckel-Gruber syndrome is that of large, echogenic kidneys in association with anhydramnios and an encephalocele or other major intracranial abnormalities such as anencephaly, severe hydrocephalus, or Dandy-Walker malformation. Polydactyly may not be detected prenatally if visualization is poor with oligohydramnios, which may be present from as early as 14 weeks' gestation.[88] Diagnosis early in gestation, between 11 and 14 weeks, may be easier, because the liquor volume should be normal at this stage, examination of the fetal brain is easier, and kidneys are usually enlarged early in pregnancy.[89,90] Prenatally, the major differential diagnosis is that of trisomy 13, which may also manifest with intracranial abnormalities in the presence of large bright kidneys, cardiac anomalies, and polydactyly.

The prognosis is awful for a fetus with Meckel-Gruber syndrome. Neonatal death occurs within a few hours of life as a result of renal failure and pulmonary hypoplasia.

BARDET-BIEDL SYNDROME

Bardet-Biedl syndrome, also called Laurence-Moon-Bardet-Biedl syndrome (LMBBS), is a genetically heterogeneous disorder characterized by polydactyly, obesity, developmental delay, hypogonadism, and a rod-cone dystrophy (atypical retinitis pigmentosa).[91] Renal abnormalities are present in up to 90% of cases, and renal failure occurs in up to 60%.[92,93] Polydactyly may be the only feature that is obvious at birth. The retinal dystrophy is progressive and often is not detected until the child is at school, and, although the renal changes may be detected earlier, they rarely cause early symptoms. Prenatally, large, echogenic kidneys are the most common presenting feature. This finding should prompt a search for polydactyly, which is present in 70% of cases, and cryptorchidism in a male fetus. To date, 12 loci have been identified (BBS1 through BBS12), with at least 50% of the families tested mapping to 11q13 (BBS1).[94] Although BBS is considered an autosomal recessive syndrome, it has been further delineated to suggest a "triallelic" mode of inheritance, in which three mutant alleles are required to manifest the phenotype.[95] In sporadic cases, definitive diagnosis must await postnatal investigations. In families with a previously affected child, detection of large, "bright" kidneys and polydactyly can be used diagnostically.

CONGENITAL FINNISH NEPHROSIS

The autosomal recessive disorder known as congenital Finnish nephrosis usually leads to death in early infancy, although recent treatment protocols have allowed longer survival and subsequent renal transplantation. It is relatively common in Finland, where the incidence is 1 in 10,000 births, but it is less common elsewhere. The first clue to the diagnosis often follows routine measurement of maternal serum alpha-fetoprotein (AFP) as part of a screening test for spina bifida or Down syndrome. The maternal serum AFP is very elevated (40 to 60 multiples of the median [MoM]). The amniotic fluid AFP is also greatly increased, and more detailed analysis of the amniotic fluid shows markedly increased levels of protein, including albumin and immunoglobulin G.[96] The kidneys usually appear normal on scans, but a large placenta and peripheral edema of the fetus may be noted, although this is usually a later finding. Histologic findings include an increase in mesangial matrix and tubular microcysts. Mutations have been detected in the nephrin gene on chromosome 19q13.1, and prenatal diagnosis is available for known families through chorionic villus sampling.[97]

ELEJALDE SYNDROME

In 1977, Elejalde and coworkers described a spectacular overgrowth syndrome in two siblings with birth weights approximately twice that expected, 7500 g at term and 4300 g at 34 weeks.[98] Subsequent reports showed similar overgrowth, with the placenta included in the size discrepancy. The inheritance is autosomal recessive, and early neonatal death is usual. The main features include a swollen, globular body with redundant neck skin, exomphalos or an umbilical hernia, short limbs, craniosynostosis and intracranial anomalies, postaxial polydactyly, and a hypoplastic nose. The kidneys are large and cystic.[99]

FRASER SYNDROME

Fraser syndrome is a rare, autosomal recessive disorder characterized by cryptophthalmos, syndactyly, and renal agenesis or obstructive uropathy.[100] The cryptophthalmos is present in 85% and is bilateral in 70% of these cases. Syndactyly occurs in approximately 80% of cases and may be partial or complete. Renal agenesis is present in 85%; it is unilateral in 37% and bilateral in 47% of cases. Developmental delay occurs in about 80% of survivors, although this condition is usually lethal. Cleft lip and palate occur in 10% and may be detectable on an anomaly scan.[101] The gene for this disorder has not been located, but suspicion may be raised at the time of a 20-week anomaly scan if the renal lesion is unilateral and the associated eye and hand abnormalities are suspected. If renal agenesis is bilateral, oligohydramnios may preclude further assessment, and a full postmortem examination would be required for the correct diagnosis.

BRANCHIO-OTO-RENAL SYNDROME

The autosomal dominant disorder known as branchio-oto-renal (BOR) syndrome comprises conductive and sensorineural deafness, branchial fistulas, and renal anomalies that include duplication of the collecting system, hydronephrosis, cystic kidneys, and unilateral or bilateral renal agenesis. There is considerable variation in expression and penetrance in this disorder, so a detailed family history is important. Without a family history, the diagnosis would be difficult to make prenatally. Mutations in the gene *EYA1*, located at 8q13.3, have been shown to be responsible in some cases.[102] A definitive prenatal diagnosis is unlikely in low-risk cases, because the associated findings can be very subtle.[103]

ECTRODACTYLY, ECTODERMAL DYSPLASIA, AND CLEFTING SYNDROME

The ectrodactyly, ectodermal dysplasia, and clefting (EEC) syndrome is an autosomal dominant disorder characterized by a lobster-claw limb anomaly (ectrodactyly), which may be present in one or more limbs, cleft lip and palate, and ectodermal dysplasia. Expression can be extremely variable, and the syndrome may occur as a new mutation. Ectodermal dysplasia is manifested as pale, thin, sparse hair and may include abnormal or missing teeth.[104] Moderate to severe hydronephrosis, renal duplication, hypoplasia, and dysplasia are among the spectrum of renal abnormalities that occur in up to 50% of these cases, and sonographic diagnosis has been reported in a number of cases.[105,106] A family history and a careful search for clefting or limb anomalies should make this diagnosis clear. Linkage studies have located gene susceptibilities at 7q11.2-q21.3 and (Online Mendelian Inheritance in Man [OMIM] Reference 129900) and 3127 (OMIM 604292), but mutation analysis is not yet available.

SCHINZEL-GIEDION SYNDROME

The autosomal recessive condition termed Schinzel-Giedion syndrome comprises severe midface retraction, skull anomalies, talipes, and cardiac and renal malformations. There is frontal bossing, which, together with midface retraction and chubby cheeks, gives the face a "figure 8" shape. Death usually occurs before 18 months. Gross congenital hydronephrosis (>80 mm) may be the presenting feature, usually late in the second trimester.[107] This is often the main prenatal feature, although careful inspection may reveal mesomelic shortening of the lower limbs, bowing of the long bones, postaxial polydactyly, and talipes. Cardiac anomalies are most commonly atrial septal defects (ASD) and patent ductus arteriosus (PDA).

DIGEORGE SYNDROME (22Q11 DELETION)

DiGeorge syndrome results from interstitial deletions of chromosome 22q11 and comprises congenital heart anomalies, cleft palate, neonatal hypocalcemia, and absent thymus with T-cell abnormalities. Other anomalies include talipes and thumb duplication. Goodship and colleagues[108] reported three cases that manifested with renal anomalies on prenatal ultrasound. Two had MCDKs with oligohydramnios, and one had unilateral hydronephrosis with ureterocele. Cardiac anomalies were found in two of the three cases. All three died, and aplasia of the thymus found at postmortem examination prompted the search for 22q11 deletion. Although it may not be appropriate to recommend 22q11 analysis in all cases of fetuses with renal anomalies, it should be offered if an associated cardiac defect is detected.

ZELLWEGER (CEREBRO-HEPATO-RENAL) SYNDROME

Zellweger (cerebro-hepato-renal) syndrome is an autosomal recessive disorder of peroxisome deficiency. The phenotype may be caused by mutations in any of several different genes involved in peroxisome biogenesis. Infants with this disorder are characteristically severely hypotonic at birth and may have nystagmus and seizures. Many die within the first year of life.[109] Other features are hepatomegaly and liver dysfunction, dysmorphic features including a high forehead, developmental delay, and renal cortical cysts. Prenatally, multiple renal cysts may be seen bilaterally, as may cerebral ventriculomegaly, which may be associated with agenesis of the corpus callosum (20%) and micropachygyria (67%). Magnetic resonance imaging may facilitate diagnosis,[109] and, as the pregnancy progresses, it may also be possible to demonstrate reduced fetal movements. Prenatal diagnosis is usually by quantification of very-long-chain fatty acids (VLCFAs) on chorion villus biopsy.[110]

RENAL CYSTS AND DIABETES (RCAD) SYNDROME

Diabetes during pregnancy is associated with a number of fetal malformations, including neural tube, skeletal, heart, and urogenital defects, particularly renal agenesis. Recent reports have also linked congenital renal cystic disease and diabetes to mutations in the hepatocyte nuclear factor 1b (HNF1B) gene.[111,112] Mutations in this gene are associated with early-onset diabetes, and Bingham and colleagues described several families with additional dominantly inherited glomerular cystic kidney disease.[111] In view of this association, a detailed family history for diabetes should be taken if renal dysplasia is detected prenatally.

URINARY TRACT DILATATION

Dilatation of the urinary tract may be confined to the renal pelvis and/or the ureter *(upper tract)*, or it may include the bladder and urethra *(lower tract)*. When it affects the upper tract, it may be unilateral or bilateral. As with other renal tract abnormalities, dilatation may occur in isolation or in association with extrarenal anomalies. Karyotyping should be considered, as described earlier. Defining the underlying diagnosis after prenatal detection of a dilated renal pelvis may not be possible until after delivery, when postnatal ultrasound, cystourethrography, and functional imaging studies are performed; however, clues to inform prenatal counseling may lie in the detailed assessment of the rest of the fetal renal tract and extrarenal structures.

Upper Tract Dilatation

Dilatation of the upper urinary tract, with or without dilatation of the ureters, accounts for approximately 50% of all prenatally detected renal abnormalities.[113] Between 1% and 2% of pregnancies show transient or mild RPD, but this often resolves during pregnancy or after delivery. Diagnosis of dilatation of the fetal renal pelvis *(pyelectasis)* provides a continuing challenge to both prenatal and postnatal management.[114] The detection of RPD by ultrasound has gained importance for two main reasons: first, as a marker for aneuploidy, and, second, as a precursor of postnatal urinary tract pathology.

The consequences of dilatation of the upper tract stem from damage to the renal parenchyma and impairment of renal function, with histologic damage related to the degree, level, and duration of dilatation. Apoptosis leads to renal atrophy, with dysplasia resulting if impairment develops early in pregnancy.[115,116] Later-developing or partial dilatation is less likely to affect the parenchymal structure.[117] Unilateral dilatation results in a reduction in the ipsilateral GFR and an increase in the contralateral GFR.

Impairment to urinary flow can occur at any level in the urinary tract and may affect one or both sides. The common causes are pelviureteric junction (PUJ) anomaly, vesicoureteric junction (VUJ) anomaly, ureterocele (which may be associated with duplex systems), and outflow obstruction such as posterior urethral valves (PUV), reflecting the points at which the embryologic components of the urinary tract combine. Follow-up studies have suggested that significant renal pathology exists in a variable proportion of neonates, with some studies reporting a low incidence of only 1 in 500 pregnancies[118] and others up to 1 in 300 pregnancies.[119] In one study, 142 neonates were found to have RPD over a 6-year period from 1979 to 1985, and 110 (78%) of these cases were detected by prenatal sonography. Of these, 41% had PUJ anomalies, 23% had primary megaureter, 13% had duplex systems with upper pole dilatation, and 10% had PUVs.[120] A comparison with 146 neonates presenting symptomatically with abdominal masses or urinary tract infection over the preceding 30 years showed significant differences in the causes of RPD, suggesting that prenatal sonography demonstrates more accurately the true incidence of congenital anomalies of the urinary tract. Although some infants with prenatally diagnosed upper tract dilatation would have been asymptomatic and undetected in the presonography era, the ability to detect significant pathology may improve outcome for others by enabling early postnatal or even in utero intervention.

Degrees of Renal Pelvis Dilatation

The fetal renal pelvis can be measured in three planes: anterior-posterior (AP), transverse, and longitudinal (Fig. 4-7). The renal pelvis is often difficult to visualize and is readily seen only after the AP diameter is 2 mm or greater. There have been a number of studies defining the upper limit of normal,[114] but a general consensus is yet to be reached. A reasonable approach is to consider greater than 5 mm diameter before 30 weeks' gestation and greater than 7 mm after 30 weeks' gestation as the upper limit of normal. Moderate dilatation may be considered if the AP diameter exceeds 10 mm, with severe dilatation defined as greater than 15 mm at any gestational age (Table 4-6).

Fetal RPD may be unilateral or bilateral, but is more frequently reported as bilateral. There is also a marked sex

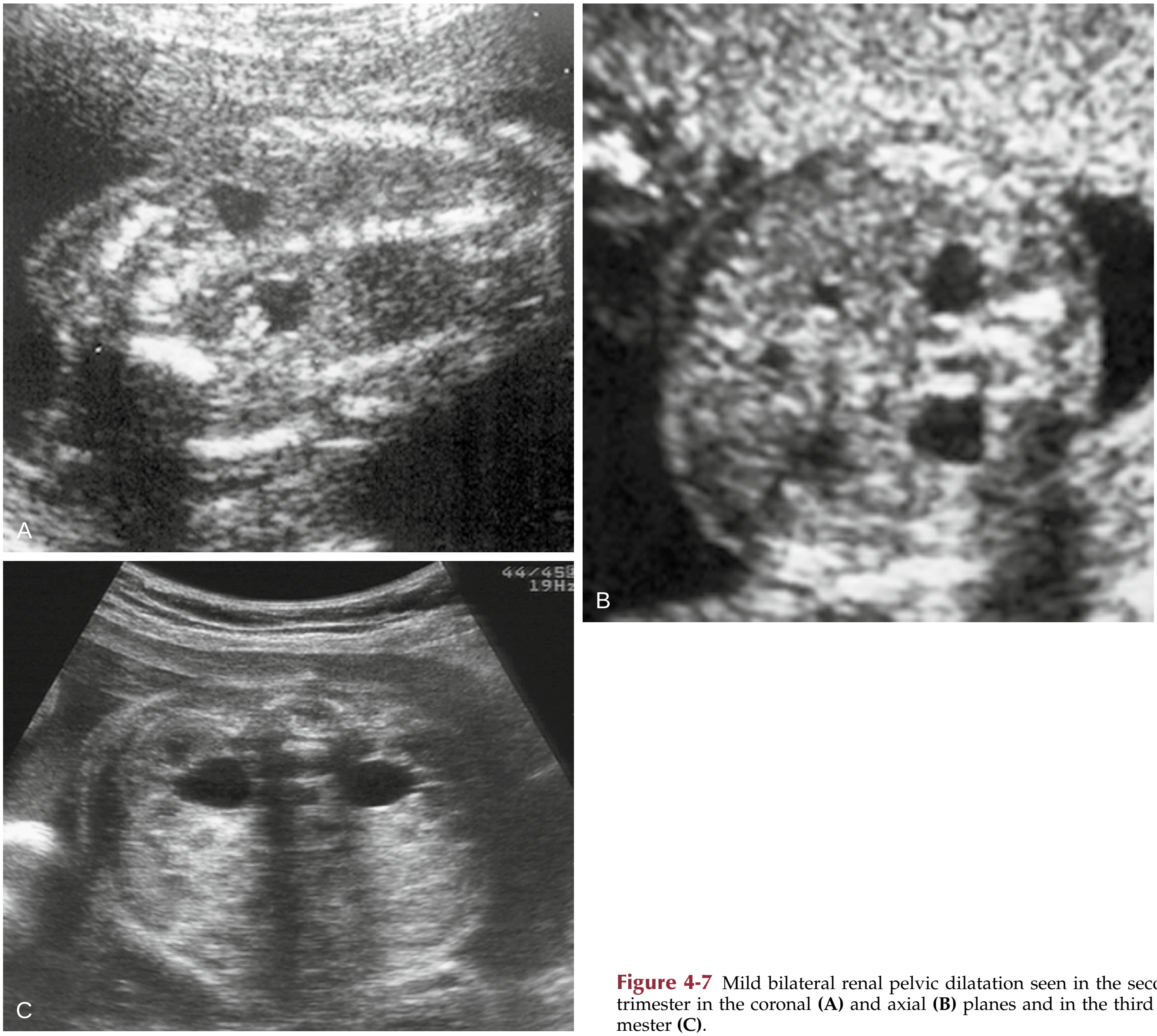

Figure 4-7 Mild bilateral renal pelvic dilatation seen in the second trimester in the coronal **(A)** and axial **(B)** planes and in the third trimester **(C)**.

difference with a male-to-female ratio of about 2:1.[121-123] Other factors, such as maternal pyelectasis[124] and filling of the fetal bladder, are also said to influence pelvic size.[125]

Mild Renal Pelvis Dilatation and Aneuploidy

Once upper tract dilatation in the fetus has been identified, a detailed anomaly scan should be performed to exclude the presence of other extrarenal abnormalities. The identification of another anomaly or the presence of other risk factors such as older maternal age or positive screening for Down syndrome should prompt the offer of fetal karyotyping.[123,126,127] Most series currently reported do not take these other risk factors into account when reporting their data. Analysis of 737 fetuses with mild RPD recruited from an unselected population of 101,600 births showed that, when RPD was present as an isolated finding in fetuses of women younger than 36 years of age, the risk of aneuploidy was 0.33%, whereas, for women older than 36 years, it was 2.22%.[123] Another approach has been to estimate the increased risk conferred by the finding of mild RPD and adjust the prior risk by this factor. Pilu and Nicolaides used this approach to suggest that isolated RPD confers a risk of trisomy 21 that is 1.5 times the background risk.[128] However, not all authors concur with this view. In a series of 1177 fetuses with mild RPD recruited between 16 and 26 weeks of gestation, 5 fetuses from a total of 805 with apparently isolated RPD had trisomy 21. The expected frequency of trisomy 21 in the population was estimated as 0.40%, which was not significantly different from the observed frequency of 0.62%.[8]

The widespread incorporation of first-trimester and early second-trimester Down syndrome screening into routine prenatal care has implications for the role of second-trimester minor markers of aneuploidy such as RPD in assessing the risk for aneuploidy. In 1998, Thompson and Thilaganathan reported on a prospective study evaluating the significance of isolated RPD in an unselected population in which first-trimester nuchal translucency measurement, second-trimester maternal serum biochemistry, and second-trimester ultrasound screening were offered.[129] A total of 20 cases of trisomy 21 were detected. Of these, 14 were identified through

Table 4-6 Causes of Upper Tract Dilatation

Renal Causes	Extrarenal Causes
Pelviureteric junction anomaly	Sacrococcygeal teratoma
Vesicoureteric junction anomaly	Hydrometacolpos
Posterior urethral valves	Other pelvic masses
Duplex systems	
Ureterocele/ectopic ureter	
Urethral atresia	
Cloacal anomaly	
Vesicoureteric reflux	
Megaureter	
Megacystis microcolon hypoperistalsis syndrome	

screening before the 18- to 23-week anomaly scan, 2 were associated with multiple markers, and 4 were detected postnatally. RPD, defined as an AP pelvis diameter greater than 4 mm, was detected as an isolated finding in 423 second-trimester pregnancies (3.9%). None of the fetuses with isolated RPD was affected with Down syndrome.

Natural History of Renal Pelvis Dilatation

Sairam and associates, using a range of 4 to 6 mm AP diameter to define mild RPD, showed a prenatal resolution rate of 80% (152/191 cases).[130] Chitty and coworkers, in a study of 475 cases of mild RPD (AP diameter, 5 to 10 mm) detected between 16 and 26 weeks' gestation and re-evaluated in the third trimester, supported this view.[131] The degree of dilatation remained mild (<10 mm) or improved in 66.1% of cases. The tendency of prenatally detected RPD to resolve is supported by the normal postnatal renal appearances reported in 36% to 80% of cases followed up within the first year of life.[122,130-133] However, prenatally detected RPD is of significance as an indicator of urinary tract pathologies including pelviureteric junction obstruction (PUJO), VUR, early signs of outflow obstruction, duplex systems, multicystic dysplasia, and upper tract dilatation in the absence of obstruction. Reflux detected during investigations for prenatal RPD is found more commonly in males[134,135] in contrast to reflux that presents clinically, and is associated with renal scarring, which is usually seen in girls. It may be that reflux in the prenatal group is primarily anatomic in origin, possibly related to bladder dysfunction in male fetuses. It is therefore debatable whether reflux associated with prenatal RPD is clinically significant in all cases.

The timing of the postnatal investigations can influence the detection of renal changes. Early in the newborn period there is a state of relative oliguria, and renal ultrasound scans can give a high incidence of false-negative results. Some studies have suggested that all fetuses with prenatal RPD should be rescanned at a few months of age, even if the initial scan was normal, so as not to miss any possible pathology.[136] Identifying those cases most at risk of postnatal pathology requires reassessment of the renal pelvis in the third trimester and selection of those cases in which dilatation persists. Most commonly, a cut-off of 10 mm AP diameter is used to identify the potentially significant dilated third-trimester renal pelvis. Many authors describe an association between prenatal RPD, defined as an AP pelvis greater than 10 mm in diameter, and urinary tract surgery,[130-131,133,137] but data relating specifically to second-trimester mild RPD and surgery are more difficult to derive. In studies in which serial scanning was performed prenatally, progression of dilatation was predictive of a worse outcome. Wickstrom and colleagues reported that 55% of infants requiring surgery in their study had demonstrated a progression of dilatation in utero.[9] Chitty's group found that, among those fetuses identified with RPD of 5 to 10 mm in the second trimester, those whose dilatation progressed to greater than 10 mm in the third trimester had a higher incidence of pathology than those whose dilatation resolved or remained less than 10 mm.[131]

Management during Pregnancy

The detection of prenatal RPD should prompt a detailed anomaly scan looking for extrarenal anomalies and other markers of aneuploidy. In the light of the findings, invasive testing should be discussed with the parents, taking into consideration other factors such as maternal age and any prior screening tests for Down syndrome. The urogenital tract should be examined carefully to exclude other pathologies such as a duplex system or MCDK. The bladder should be carefully examined to ensure that it empties and fills normally and that there is no thickening of the bladder wall consistent with outflow obstruction. Prediction of outcome after a single scan is not possible, but parents should be reassured that this is a common finding and that the risk of serious sequelae is very small.

A repeat scan should be performed in the early third trimester or after about 6 to 8 weeks. If the dilatation has resolved, in our unit we offer no further investigation, because the risk of any clinically significant pathology is extremely small. If the dilatation is still present, and particularly if the AP diameter has increased to greater than 10 mm or other renal pathology is suspected, the pediatricians should be alerted and postnatal scans and other investigations initiated as clinically indicated. In these cases, referral to a pediatric urologist or review in a combined fetal medicine/pediatric urology clinic may be helpful. Any potential abnormality detected in pregnancy is a source of great anxiety to the parents, and counseling in a combined clinic may help minimize the anxiety caused. If prenatal sonography shows severe bilateral dilatation of the urinary tract associated with poor echogenicity of the renal parenchyma and oligohydramnios, termination may be considered, with a multidisciplinary approach to discuss the prognosis and options for management with the parents.

Postnatal Management of Upper Tract Dilatation

The extent of postnatal investigations that should be performed in the presence of persistent fetal RPD remains under debate. Whereas aggressive management can detect more clinically silent "pathology" (e.g., reflux), the clinical significance of these findings remains unclear in most cases.[135] At birth, the neonate is often prescribed prophylactic antibiotics to prevent urinary tract infection and an ultrasound scan of the urinary tract at 3 to 5 days of age, together with contrast cystography in the male infant to exclude PUV and reflux if there has been a dilated bladder or moderate bilateral dilatation. Micturating cystography can be delayed in females until 7 to 10 days of age. At 4 to 6 weeks in both sexes, a dynamic isotope study (MAG3 or DMSA) may be performed to establish whether the dilatation is related to an active impairment of urinary flow or is the sequela of a past event.

Conservative management with continuation of prophylactic antibiotics is all that is necessary for the majority of these

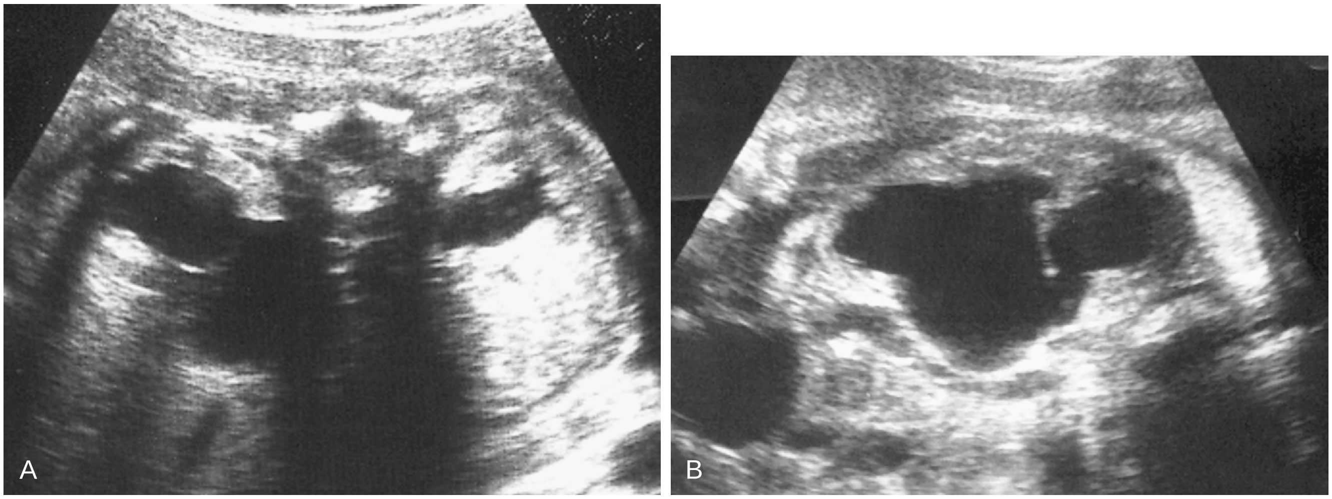

Figure 4-8 Images of a fetus with bilateral pelviureteric junction obstruction, with asymmetric dilatation demonstrated in the axial plane **(A)**. The sagittal view **(B)** demonstrates the dilatation of the pelvis, which ends abruptly at the junction with the ureters, giving the classic "Mickey Mouse ears" appearance.

infants, because spontaneous improvement or resolution is the most common outcome. However, regular follow-up with repeated ultrasound scans and isotope studies is needed during the first 2 years of life to ensure that the spontaneous evolution is satisfactory. Fewer than 20% of children presenting with significant prenatal dilatation of the upper urinary tracts will require surgery. The incidence among those presenting with mild pyelectasis is much lower, and surgery is usually confined to those in whom dilatation increased to greater than 10 mm.[131,138]

Pelviureteric Junction Anomalies

Fetal uropathies occur in 1 of every 600 to 800 pregnancies, and PUJ anomalies are the most common type, accounting for 35% of prenatally detected uropathies,[7] with an incidence of 1 in 2000 live births.[139] Males are more commonly affected, with 90% of cases occurring unilaterally. There are three types of PUJ anomalies: extraluminal, luminal, and intraluminal. Extraluminal anomalies are commonly caused by aberrant vessels, although kinks, bands, adhesions, and arteriovenous malformations have also been described, spanning the PUJ and reducing the urine flow intermittently.[140,141] In these cases, the dilatation of the pelvis and symptoms are often intermittent. Luminal anomalies are the most common type and are caused by abnormal distribution of the muscular and collagen fibers at the level of the PUJ. Intraluminal anomalies are rare and are mainly described as valve-like processes and benign fibroepithelial polyps.[113]

Sonographic Diagnosis and Management

A definitive diagnosis of PUJ anomaly cannot be made until after birth. However, the diagnosis may be suspected prenatally if RPD is seen without ureteric dilatation, and with a normal bladder appearance (Fig. 4-8). Liquor volume is usually normal. Differential diagnoses include multicystic renal dysplasia, obstruction from the lower urinary tract, renal cysts, and perinephric urinomas. As obstruction progresses, the renal cortex becomes thinner, and associated dysplasia may manifest with increased cortical echogenicity or cortical cysts or both. Serial ultrasound scans are recommended during pregnancy to assess the degree and progression of dilatation, because this may correlate with postnatal renal function.[142]

Outcome is generally good for both unilateral and bilateral disease, but occasionally oligohydramnios develops in association with bilateral disease and worsens the prognosis, so careful monitoring is required. Prenatal intervention (e.g., shunting an extremely dilated renal pelvis) is very rarely required. Serial sonography during pregnancy may help to inform both parents and pediatricians as to the likelihood of requirement for surgical intervention, but ultimately this decision will be undertaken after postnatal investigation. The infant should be placed on prophylactic antibiotics while these tests are carried out, to minimize the risk of urinary tract sepsis.

It is important to define whether the PUJ anomaly is an isolated condition or is associated with other anomalies. Twenty-five percent of cases are associated with other renal abnormalities, including renal agenesis, multicystic renal dysplasia, VUR, ureteric hypoplasia, partial or complete ureteric duplication, and horseshoe kidney, and some have other, extrarenal abnormalities, such as anorectal anomalies, congenital heart disease, or VATER syndrome.

Vesicoureteric Junction Obstruction Anomalies

VUJO anomalies account for about 10% of prenatally detected instances of upper tract dilatation, with an approximate incidence of 1 in 6500 live births.[139] The male-to-female ratio is approximately 2:1, and up to 25% of cases are bilateral.[143]

Diagnosis

Prenatal sonography shows a dilated ureter, which may be seen communicating with the dilated renal pelvis (Fig. 4-9). The bladder appearance and liquor volume are normal. The main differential diagnoses are VUR and ureteric obstruction due to ureterocele associated with a duplex kidney (Fig. 4-10). Coexisting abnormalities occur in 16% of cases and include PUJO, multicystic renal dysplasia, pelvic kidney, renal agenesis, and VUR.[144]

Vesicoureteric Reflux

VUR is a permanent or intermittent retrograde flow of bladder urine into the upper urinary tract; it occurs either as a primary abnormality in an anatomically normal bladder or

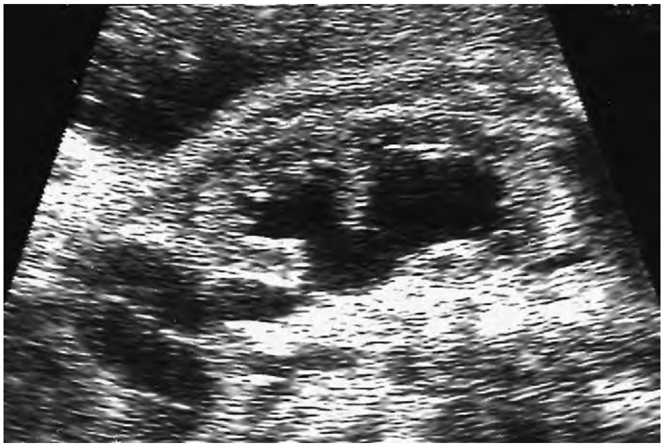

Figure 4-9 Ultrasound image showing a dilated ureter and pelvis in a fetus with suspected vesicoureteric junction obstruction subsequently found to have vesicoureteric reflux.

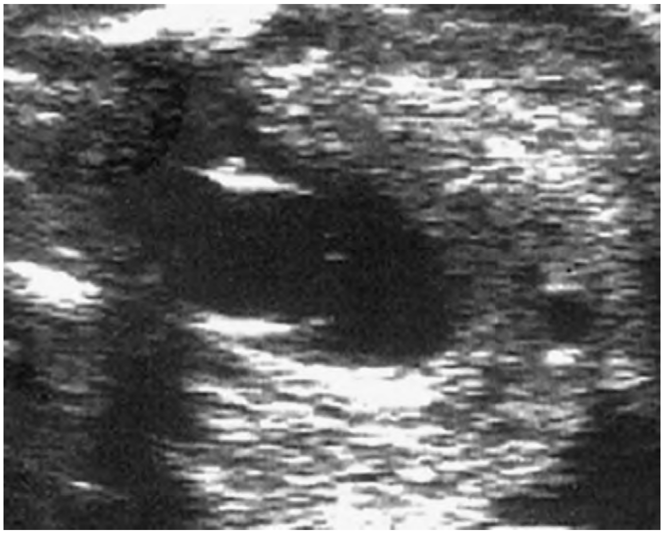

Figure 4-10 Axial view through the bladder demonstrating a ureterocele.

secondary to another cause of urine flow impairment or bladder neuropathy. The incidence in the general pediatric population is 1% to 2%, and it is usually diagnosed in infants being investigated for urinary tract infection.[145] The associated predisposition to infection can lead to significant morbidity due to scarring and chronic renal dysfunction. VUR accounts for approximately 10% of all instances of prenatally diagnosed RPD, and the sonographic findings may be limited to RPD, although bilaterally dilated ureters and bladder may be seen in severe cases (Fig. 4-11). It is not possible to make a definitive diagnosis in utero. More than 80% of children with prenatally diagnosed reflux are boys.[135,146,147] In contrast, the postnatal incidence of reflux has a female-to-male ratio of 5:1.[148] The increased voiding pressure required in boys, which in utero may distort the ureterovesical junction, is a possible explanation for this.

VUR may be associated with other renal abnormalities, in particular ureteroceles in duplex kidneys, PUJ anomalies, multicystic renal dysplasia, and unilateral renal agenesis.[149] Prenatal sonography may not be able to assess these definitively, so all infants should be carefully assessed in the postnatal period. For prenatally diagnosed VUR, the dilatation may be confirmed postnatally with ultrasound, but this is not reliable.[135] Micturating cystogram should be carried out to confirm the presence of reflux. If reflux is suspected, it is important to proceed postnatally to a DMSA isotope scan, so that individual renal function and the presence of renal scarring can be assessed. Approximately 60% of kidneys with significant degrees of reflux show an abnormal renogram within the first 4 weeks of life, before a urinary tract infection had occurred in the majority of cases.[145,150] These data suggest that abnormalities in renal development with reflux occur during intrauterine life.

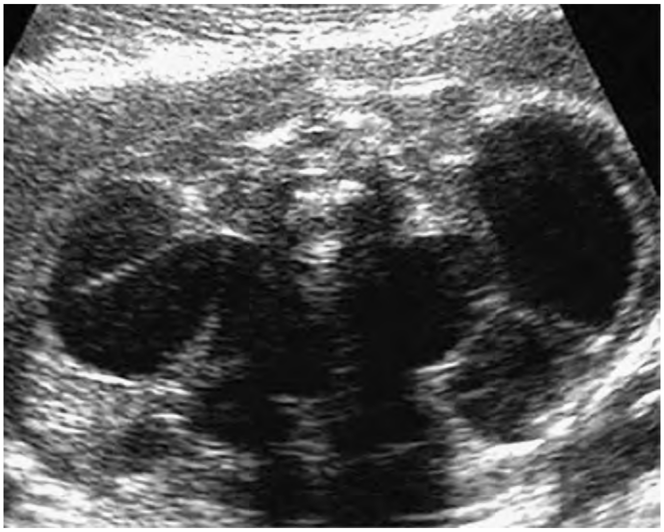

Figure 4-11 Axial view through the abdomen of a fetus with bilateral megaureters.

Duplex Kidneys

A duplex system occurs when the kidney is divided into two separate pelvicalyceal systems, or moieties, with either complete or partial duplication of the ureters (Fig. 4-12). Duplex systems are one of the more common renal anomalies, occurring in the general population with an incidence of 1:125 in postmortem studies.[151] Many individuals with a duplex kidney are asymptomatic, but a proportion present in early infancy or childhood with complications such as urinary tract infection.[152] Antibiotics may be used to treat complications, but a number of children with recurrent problems and a poorly functioning moiety may require surgery. For prenatally diagnosed duplex kidneys, the natural history is uncertain, and it is therefore common practice to treat prophylactically with antibiotics, so as to potentially reduce the risk of complications while the diagnosis is confirmed and the degree of any renal dysplasia is assessed.

Sonographic Diagnosis

Prenatal ultrasound has not always proved reliable in accurately distinguishing duplex kidneys from a range of other disorders causing renal dilatation. Differential diagnoses include hydronephrosis, polycystic kidneys, solitary renal cysts, and PUJO.[153] Abuhamad and colleagues described features that were more accurately associated with a duplex kidney, including two separate, noncommunicating renal pelves (see Fig. 4-12A), dilated ureters (see Fig. 4-12B), cystic structures within one pole (see Fig. 4-12F), and one or more echogenic cysts in the bladder, representing ureterocele (see Fig. 4-10).[154]

Detection may be enhanced in a multidisciplinary setting. In a cohort of patients seen at a tertiary referral renal clinic at University College Hospital between 1992 and 2000, 39 (81%) of 48 women in whom a fetus with a duplex system was strongly suspected had that diagnosis confirmed postnatally.[155] Detection of a ureterocele was most strongly associated with a correct diagnosis of duplex kidney, with 26 (88%) of 30 prenatally detected ureteroceles subsequently found to be associated with a duplex system. Where a prognostic feature such as a dilated moiety, dilated ureter, or ureterocele was seen in addition to the detection of two separate moieties, positive correlation was found between the number of features seen and the subsequent confirmation of a duplex system (64% for one, 80% for two, and 85% for three features seen).[155]

Significance of Prenatal Detection of Duplex Systems

The impact of prenatal detection of duplex systems is still being determined. Hulbert and Rabinowitz studied 79 children with severe hydronephrosis associated with a duplex system. Of 20 children diagnosed prenatally, conservative surgery with renal salvage was possible in 13 (65%); this represented no significant improvement over the remaining 59 children who presented clinically, of whom 34 (58%) underwent renal salvage.[156] A study of 29 patients treated for ectopic ureter or ureterocele found that conservative surgical procedures were possible in 5/13 (38.5%) of those whose condition was detected prenatally, compared with only 2/16 (12.5%) of those presenting clinically, with the remainder undergoing upper pole nephrectomy. Only one of those in the prenatally detected group had symptoms, compared with 14/16 (87.5%) of the remainder.[157]

Long-term follow up over 8 years of a group of 52 infants with prenatally detected duplex system ureteroceles assessed the outcome of expectant management in 14 cases in which upper pole function was less than 10% and the lower pole was unobstructed, with reflux not exceeding grade III and an unobstructed bladder. Prophylactic antibiotics were used until completion of toilet training or to the age of 5 years if reflux persisted. In six cases, the hydronephrosis resolved and the ureterocele collapsed; none of this group developed symptoms or required surgery. Of the 38 remaining patients who underwent surgical treatment, 13 required subsequent unplanned secondary procedures.[158] A more recent comparison of clinical outcome for prenatally and postnatally diagnosed infants with duplex kidney carried out in our unit suggested that prenatal diagnosis may not reduce the need for surgery but does result in earlier, less complex, and more definitive surgery, with a consequent small reduction in long-term bladder dysfunction.[159]

Prenatal and Postnatal Management

The natural history of prenatally diagnosed duplex kidneys remains uncertain, and prenatal diagnosis at present does not distinguish between those who would eventually have presented clinically with complications and those who would have remained asymptomatic. For those duplex systems diagnosed prenatally, prophylactic antibiotics are used until the nature of the duplex system is defined during postnatal investigation, as for other urinary tract dilatations. For simple duplexes (i.e., no dilatation of either moiety) where there is no evidence of obstruction or reflux, no treatment is needed. Treatment of complex duplex systems depends on which moiety of the affected kidney is dilated, the aim of all treatment being to conserve as much normal renal parenchyma as possible.

Ureterocele

Ureteroceles consist of cystic dilatations of the submucosal segment of the intravesical ureter with consequent narrowing of the ureteral orifice. They are associated with the upper pole of a duplex kidney in 80% of cases (see earlier discussion) but may be isolated. Ureteroceles may be identified prenatally by the detection of an echolucent circular rim within the fetal bladder (see Fig. 4-10).

Posterior Urethral Valves

Male fetuses develop PUVs due to abnormal formation of the posterior urethra. This condition results in bladder outflow obstruction. It is characterized by the presence of a distended bladder and therefore is considered in detail in the next section.

BLADDER ABNORMALITIES

Normal Sonography of the Fetal Bladder

The normal fetal bladder can be visualized from the onset of urine production, which occurs by about 10 weeks. By 12 weeks, the fetal bladder can be visualized in 100% of normal fetuses on TVUS. The diameter of the bladder at 12 weeks should be no more than 6 to 8 mm.[160] By the time of the 18- to 20-week routine anomaly scan, the bladder should be identified in 100% of cases. The normal fetus voids regularly, but the bladder is never completely empty and always contains a small residual volume. The observation of cyclic filling and emptying of the bladder forms an important part of the ultrasound assessment. In the normal bladder, the mucosa and musculature are of similar echogenicity to other structures in the pelvis, and there is little discernible space between the fluid in the bladder and, for example, paravesical arteries. The bladder wall itself should be no thicker than 3 mm.

As the pregnancy progresses, the normal bladder is imaged as an elliptical, fluid-filled structure within the fetal pelvis; it is bordered laterally by the umbilical arteries, which in the adult become the superior vesical arteries. Anterior to the bladder are the ossified pubic bones, and posterior to it is the normal rectosigmoid colon, which can be seen anterior to the sacral segment of the spine. The paravesical arteries may be used to differentiate the bladder from other cystic structures within the pelvis.

Megacystis

A distended bladder may arise for two main reasons. First, there may be obstruction to the flow of urine out of the bladder. This occurs most commonly in male fetuses, usually as a result of maldevelopment of the urethra. A spectrum of abnormalities occurs, from complete urethral atresia through to the formation of urethral valves that form around the membranous/prostatic urethra. In the female, bladder obstruction is usually the result of rather more complex defects in the development of the urogenital system, often grouped under the term “cloacal plate abnormalities” (discussed later). The second group has an enlarged bladder secondary to nonobstructive causes. This is a heterogeneous group, often with complex underlying pathology.

A distended, thick-walled bladder associated with a dilated posterior urethra and oligohydramnios is pathognomonic of PUV (Fig. 4-13), but without this combination of ultrasound signs, the underlying pathology is less certain. Prediction of other etiologies for the megacystis is less accurate, but primary reflux, cloacal plate anomalies, urethral duplication,

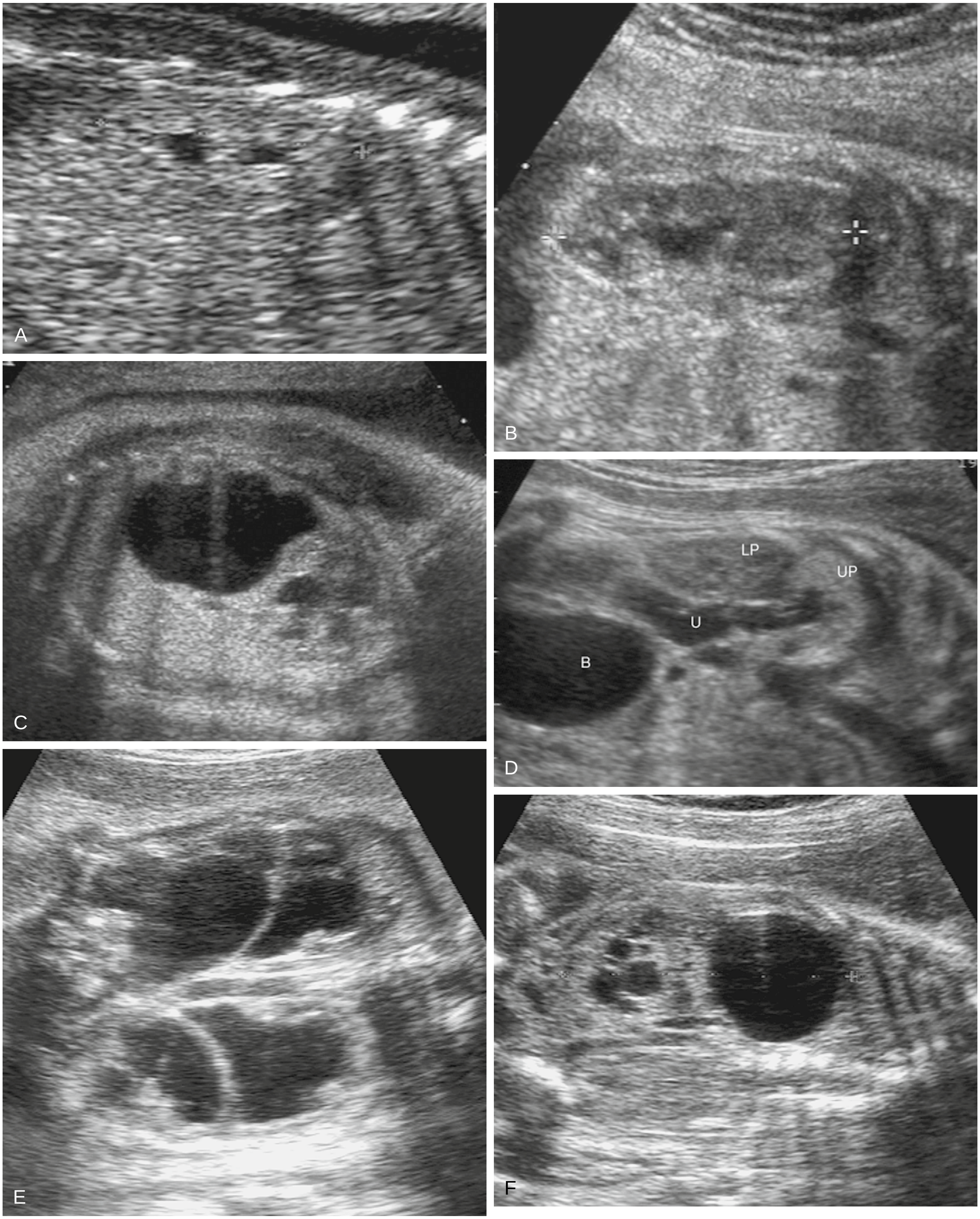

Figure 4-12 Ultrasound images of duplex systems showing a simple duplex **(A)**, a duplex with one dilated pole at 20 weeks' gestation **(B)**, and progressive dilatation at 32 weeks **(C)**. A dilated upper pole with a dilated tortuous ureter is shown in **D** (B, bladder; LP, lower pole; U, ureter; UP, upper pole). A bilateral duplex system with both poles dilated is shown in **E**. A duplex with a dilated upper pole and cystic lower pole is shown in the axial view **(F)**,

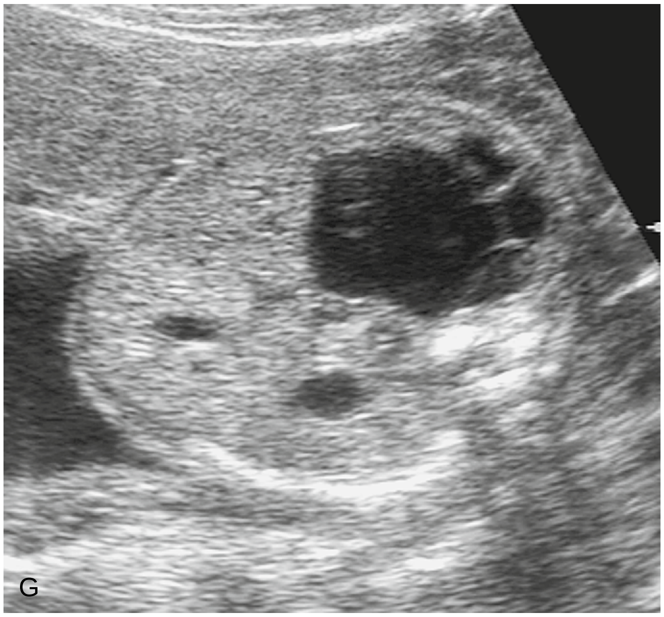

Figure 4-12, cont'd, and in the sagittal plane **(G)**.

and megacystis microcolon are included in the differential diagnosis.

In a review carried out in our own unit of 115 fetuses with persistent bladder dilatation seen over a 10-year period, 47 (41%) underwent termination of pregnancy, 61 (53%) were liveborn, and 7 (6%) died in utero.[161] Of the 47 fetuses undergoing termination, 3 had aneuploidy (trisomy 13, trisomy 21, XXYY). Sixteen of these fetuses had oligohydramnios by 20 weeks' gestation (Fig. 4-14; see Fig. 4-13), the presence of which contributed to a decision to terminate the pregnancy. A definitive postnatal diagnosis was available in 93 cases, from either postmortem data or postnatal investigations. Just over half (48/93) were caused by PUV, and almost one quarter (21/93) were associated with megaureter, VUR, or PUJO. Other causes included cloacal anomalies, complex renal abnormalities, urethral stenosis, and complex genetic syndromes including hollow visceral myopathy, oculodental digital syndrome, VACTERL association, and the CHARGE association (*c*oloboma, *h*eart disease, choanal *a*tresia, *r*etardation, *g*enital hyperplasia, and *e*ar anomalies). Of the 61 live births, there were 7 neonatal deaths. Four of these were associated with pulmonary hypoplasia and renal failure with prenatal anhydramnios. Three infants died from complications related to other congenital abnormalities, including short-ribbed polydactyly syndrome, congenital cardiac abnormality, and megacystis-microcolon-intestinal hypoperistalsis syndrome. In addition, four died before the age of 4 years from other complications of renal failure, including sepsis and end-stage renal failure. Long-term follow-up in the surviving infants revealed impaired renal function in 32% (defined by a GFR of less than 75 mL/min/1.73 m^2); a further 44% have normal renal function but have undergone repeated surgery. Of 11 survivors older than 5 years of age, 6 have abnormal bladder function.[161]

First-Trimester Megacystis

Early-onset megacystis frequently regresses spontaneously.[160] The presence of other structural abnormalities increases the risk of aneuploidy up to 40% in some series. Sebire's series defined a distended bladder one having a diameter greater than 8 mm and a ratio of bladder diameter to crown-rump length (CRL) greater than 13%. Distended bladder was identified at a frequency of 1 in 1633 fetuses at 10 to 14 weeks. Among eight fetuses with megacystis who had a bladder diameter between 8 and 12 mm and a diameter/CRL ratio between 13% and 22%, resolution occurred in seven cases; in the eighth, there was progressive dilatation. In three other cases with progressive obstruction, the bladder diameter was always greater than 16 mm and the diameter/CRL ratio greater than 28%.[160] Favre and colleagues defined megacystis as a fetal bladder diameter exceeding 6 mm and identified 16 cases (0.31%).[162] Two fetuses had oligohydramnios, but three had renal hyperechogenicity with cysts. In 6 of the fetuses, the megacystis was isolated, but in the remaining 10 there were other abnormalities such as cystic hygroma, nuchal translucency and encephalocele, mild pyelectasis, and bilateral talipes. Of the latter group, four had chromosomal abnormalities. Only one fetus from this study survived; pregnancy was terminated in 13 of the 16 cases. Postmortem examination indicated that urethral fibrostenosis was the most common cause for megacystis in early pregnancy. Oligohydramnios is relatively rare in first-trimester megacystis, because fetal urine does not make a major contribution to amniotic fluid volume until about 18 weeks' gestation. Renal changes appear to be relatively uncommon in obstruction in early pregnancy, but their presence makes the diagnosis of bladder obstruction much more likely and influences the prognosis. However, because the fetal kidneys are normally more echogenic in early pregnancy, interpretation of renal changes at this stage can be difficult unless they are extreme.

Because spontaneous resolution of dilatation in bladders up to 12 mm in diameter is usual, expectant management should be used initially. However, there may be a small group with bladders larger than 12 mm in which the condition can be relieved by aspiration of the bladder. In some cases, this appears to allow the normal relationship of the bladder to the urethra to be restored, and the bladder distention does not reoccur after aspiration. Consideration should also be given to the possibility of aneuploidy, and, if bladder aspiration is undertaken, invasive testing should include karyotyping of the fetus.

Second- and Third-Trimester Megacystis

Bladder obstruction in later pregnancy is more likely to be partial or intermittent but can have a more profound effect on amniotic fluid volume. The underlying etiology depends on the sex of the fetus. In the male fetus, PUV is undoubtedly the most common cause of urinary obstruction.

Severe lower urinary tract obstruction has two major consequences: *pulmonary hypoplasia* secondary to oligohydramnios, which can lead to death from respiratory failure soon after birth, and *renal dysplasia* resulting from persistent damage to both the lower and the upper urinary tract, which may result in chronic renal dysfunction.[161] Amniotic fluid is essential to bronchial branch development in the lungs, in particular during the canalicular phase between 16 and 28 weeks' gestation. Three mechanisms have been proposed to explain the pulmonary hypoplasia associated with oligohydramnios: extrinsic compression, lack of fetal breathing movements, and lack of pulmonary distention. The prognosis is likely to be worse in those diagnosed prenatally, especially in the presence of midtrimester oligohydramnios.

Posterior Urethral Valves

PUV occurs because of the presence within the posterior urethral wall of mucosal folds that obstruct bladder outflow, either partially or completely. Bladder distention creates retrograde

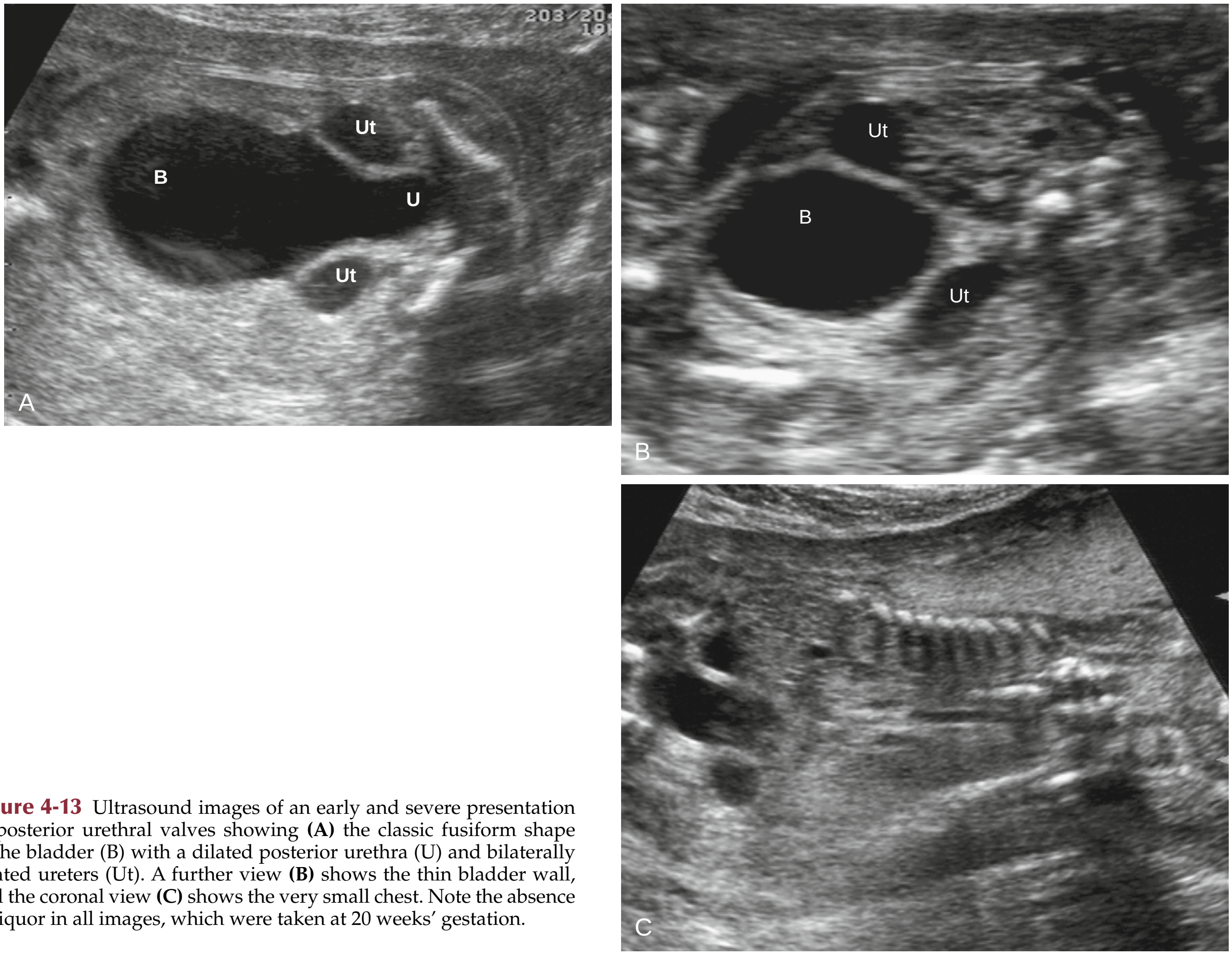

Figure 4-13 Ultrasound images of an early and severe presentation of posterior urethral valves showing **(A)** the classic fusiform shape of the bladder (B) with a dilated posterior urethra (U) and bilaterally dilated ureters (Ut). A further view **(B)** shows the thin bladder wall, and the coronal view **(C)** shows the very small chest. Note the absence of liquor in all images, which were taken at 20 weeks' gestation.

pressure in the ureters and renal pelvis, resulting in dilated ureters and hydronephrosis. If the obstruction is intermittent, the bladder wall becomes increasingly thickened and undergoes echogenic changes that indicate muscular hypertrophy. Distention of the posterior urethra above the urethral valves is represented by the so-called keyhole sign (see Fig. 4-13). Under extreme circumstances, the bladder may rupture with the development of urinary ascites. Predictive factors for use in identification of fetal urethral obstruction were described by Oliveira and colleagues.[163] In their review, 148 children with fetal hydronephrosis were admitted to a systematic protocol and prospectively monitored. A number of variables were assessed, but after final adjustment by multivariate analysis only two variables were identified as independent predictors of fetal urethral obstruction. These were oligohydramnios (odds ratio, 5; confidence interval, 1.5 to 15) and megacystis (odds ratio, 9.95; confidence interval, 2 to 14).

Cloacal Anomalies

Cloacal dysgenesis sequence is a rare cause of fetal obstructive uropathy; it usually, but not always, occurs in females.[164] In the female fetus, cloacal plate problems are associated with complex abnormalities of the genital tract and bowel abnormalities, with significant morbidity resulting. The sequence has complex pathology and characteristic features, including absent or single anal, genital, and urinary orifices together with a smooth perineum and abnormal phallic development and hydrometacolpos in the female. In addition, there may be an obstructive uropathy with hydroureters and dysplastic kidneys. Prenatal ultrasound findings in cloacal anomalies vary considerably and include transient fetal ascites, a multiloculated cystic structure arising from the fetal pelvis which may contain debris, bilateral hydronephrosis, dysplastic kidneys, intraluminal colonic calcifications, reduction in amniotic fluid volume, growth retardation, and vertebral anomalies. The combination and evolution of these findings, together with the confirmation of female karyotype, form the basis for the prenatal diagnosis of cloacal anomaly.[165]

Nonobstructive Bladder Abnormalities

Nonobstructive bladder problems are a rare and heterogenous group of complex abnormalities. To some extent, they may represent a type of neuropathic bladder, but it can be difficult to differentiate between obstructive and nonobstructive bladders prenatally. In our group of 115 infants with prenatally enlarged bladders, oligohydramnios with the development of echogenic kidneys was less common in those in whom the postnatal investigations showed no evidence of obstruction than in the group with proven obstruction.[161] Kaefer and colleagues reviewed 15 cases with similar findings.[166] Mandell's

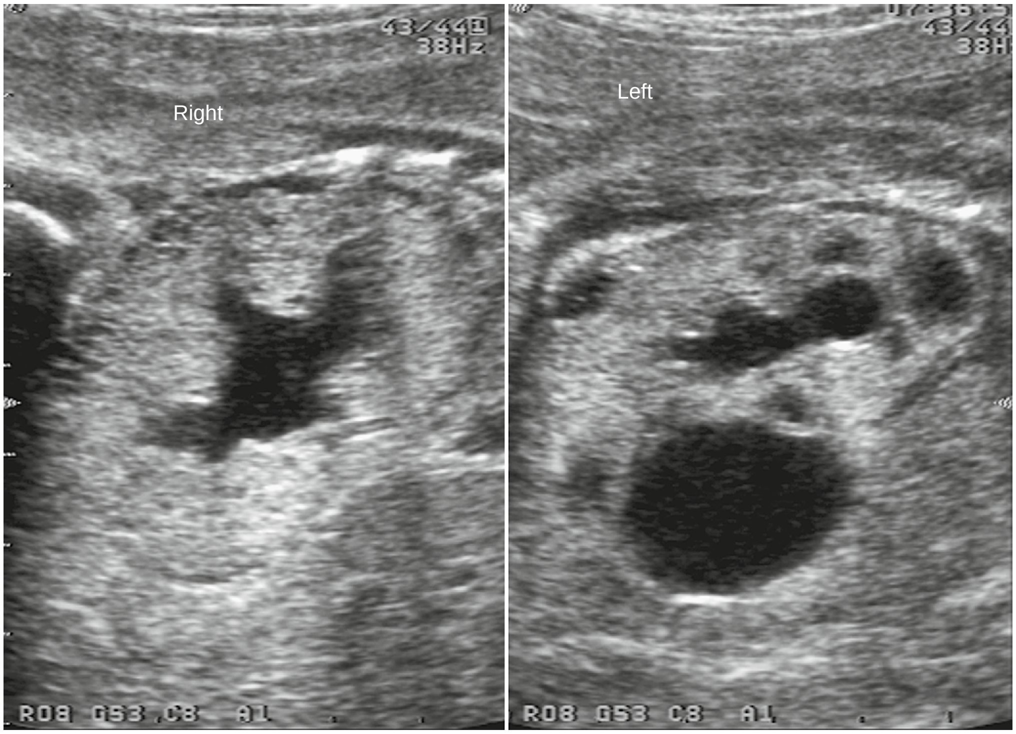

Figure 4-14 A fetus with posterior urethral valves, demonstrating the variety of cystic change seen at 29 weeks' gestation. Both kidneys are demonstrated in the sagittal plane. Both kidneys are echogenic; the right is developing small cortical cysts, and larger cysts are seen in the left kidney.

study of 11 males with in utero megacystis, hydronephrosis, and dilated ureters, who were found to have the megacystis-megaureter association after birth, supported these conclusions.[167] In all of the latter cases, a large bladder with severe reflux into dilated, tortuous ureters and dilated pelvicalyceal systems was found postnatally, leading to the conclusion that the megacystis-megaureter association can be suspected with reasonable accuracy if a large, thin-walled bladder is found together with dilated ureters and bilateral hydronephrosis but normal renal parenchyma and normal amniotic fluid volume.

Megacystic microcolon intestinal hyperperistalsis syndrome is considered to be caused by degenerative disease of smooth muscle, which causes small-intestinal obstruction, microcolon, and a large bladder. The syndrome is lethal, but, in spite of a distended bladder, it is associated with normal amniotic fluid volume and nondysplastic kidneys.

Another nonobstructive cause of bladder distention is "prune-belly syndrome." This is a rare condition associated with congenital deficiency of the abdominal musculature and associated urinary tract abnormalities. The sonographic appearances of the fetal bladder help differentiate this syndrome from obstructive uropathies. The bladder appears thick-walled and tense in cases of obstruction, whereas in prune-belly syndrome it often appears floppy. However, it may be very difficult to differentiate sonographically between urethral atresia and PUV. Increased renal echogenicity, loss of corticomedullary differentiation, and the presence of subcortical cysts indicate renal dysplasia and are poor prognostic signs.

Management of Megacystis during Pregnancy

Management of a distended bladder depends on the underlying cause and the findings at the time of presentation. Determination of fetal sex is important, because the issues are much more complex in female fetuses with a distended bladder. Consideration should be given to a cloacal abnormality, which in itself may produce severe difficulties for the fetus and long-term morbidity for the child. The appearance of a grossly distended vagina (hydrocolpos) and possibly even a distended rectum may indicate a grave prognosis. It is important, therefore, that as much information as possible is gleaned from the ultrasound examination, and a multidisciplinary team approach involving pediatric surgical colleagues is particularly appropriate in these circumstances.

The management of other causes of distended bladder depends on the underlying etiologic factors. In sacrococcygeal tumors, major problems revolve around those conditions rather than the bladder obstruction itself. However, the appearance of a distended bladder in these cases confers an graver prognosis to the underlying condition.

EVALUATION OF RENAL FUNCTION

In the second trimester, the major management decision is whether the bladder should be drained by the insertion of a vesico-amniotic shunt. Because the composition of fetal urine depends only on fetal renal function, urinalysis may have some value in determining prognosis. Normal values have been defined by obtaining urine from fetuses with an extrarenal abnormality or before termination of pregnancy,[168] observing that the composition of the urine changes with gestational age.[169] The use of urinalysis in clinical practice remains controversial because of discrepancies regarding outcome definitions and a paucity of long-term follow-up data.[170] Serial (perhaps three) bladder aspirations with an assessment of the urinary sodium, calcium, and β_2-microglobulin levels may have more value[171] in predicting long-term outcome. Survival or neonatal renal function alone cannot be the sole criterion, because renal failure and poor bladder function may ensue during childhood, with resultant long-term morbidity. A urinary calcium level greater than 8 mg/dL or a sodium concentration of greater than 100 mEq/L is generally considered to be the most sensitive prognostic indicator.[172,173] High levels of urinary β_2-microglobulin (>4 mg/L) are also predictive of renal dysplasia and renal failure by 1 year of age.[173] Fetal serum markers do not appear to have any prognostic value, with the exception of β_2-microglobulin, which does not cross the placenta. However, there are limited data available on its use in clinical practice, and measurement in utero requires fetal blood sampling, which carries an increased risk to the fetus and may not be feasible in the presence of oligohydramnios. Fetal urine concentration of cystatin C has also been proposed as a predictor of postnatal renal function, demonstrating renal tubule damage rather than damage in glomerular filtration,[174] but other predictive markers are required and may be identified as knowledge of renal development improves.[34,175]

The appearance of the fetal kidneys must also be taken into account; if they are "bright" and small, dysplasia is likely and the long-term prognosis is poor. Assessment of amniotic fluid volume forms part of the management plan; if oligohydramnios is present, the development of the respiratory system is at risk. In those cases in which amniotic fluid volume is normal or slightly reduced, it may be assumed that renal function is adequate at that point in time, provided the renal echogenicity is normal.

VESICO-AMNIOTIC SHUNTING

Consideration of bladder shunting relates to the likelihood of such a procedure's preventing the renal dysfunction and pulmonary hypoplasia that would result if persistent significant outflow obstruction persists. However, like all invasive procedures, it is not without risk, and is not guaranteed to confer an advantage to the long-term outcome. If renal dysplasia persists despite relief of the anatomic obstruction, then oligohydramnios will not be corrected and pulmonary hypoplasia will still develop. The timing of intervention is important, because long-term renal outcome will not be influenced by shunting if renal damage has already occurred in early pregnancy. Before discussion of shunting, renal function should be evaluated, as described earlier.

Vesico-amniotic shunting is performed with ultrasound guidance using a pigtail shunt. It is important that the shunt be placed as low as possible in the bladder to prevent displacement after bladder decompression; the optimal site for trocar entry is midway between the pubic ramus and the insertion of the umbilical cord. If oligohydramnios is present, an amnioinfusion may be required to provide a potential space into which to deposit the intra-amniotic end of the catheter. It may be necessary to wait for the fetus to move into an appropriate plane for an anterior approach to the abdomen, or the operator may have to manipulate the fetal trunk into position.

In 1997, Coplen reviewed the five largest series of prenatal intervention, comprising 169 cases of successful percutaneous shunt placement over 14 years. The overall perinatal survival rate after intervention was only 47%, and shunt-related complications occurred in 45% of the cases. Forty percent of survivors had end-stage renal disease.[176] Not all pregnancies exhibited pretherapy oligohydramnios, but among those that did, 56% of babies died despite intervention. Failure to restore amniotic fluid volume was associated with 100% mortality. Limiting intervention to fetuses with good prognosis appeared to improve survival and resulted in a lower incidence of renal failure among survivors. Within Coplen's review, Crombleholme[177] and Freedman[178] and their colleagues evaluated outcomes based on prognosis, as determined by fetal urine biochemistry. Fetuses with oligohydramnios were further separated into those with dysplasia and those with normal neonatal renal function. Among 45 fetuses for which intervention was successful, a poor urinary prognosis was associated with postnatal renal insufficiency in 87.5% (14/16), indicating that, even if intervention improves the chances of survival, it rarely alters the renal outcome in this group. In contrast, in the group with good prognosis, 85% (17/20) of survivors had normal renal function. When amniotic fluid returned to normal, there was no postnatal respiratory compromise, consistent with animal studies indicating that correction of oligohydramnios prevents pulmonary hypoplasia. However, because fetuses with a good prognosis may have a reasonable outcome without intervention, it is not possible, without a randomized controlled trial, to state with any degree of certainty whether in utero vesico-amniotic shunting has significant value.

Further concern over the effectiveness and value of in utero intervention was raised by Holmes and coworkers.[179] In reviewing the University of California San Francisco experience, of the 36 patients with favorable electrolytes and oligohydramnios treated by one of the three therapeutic methods over an 18-year period, only 14 (39%) had PUV, and only 8 of these infants (57%) survived. Five (63%) of eight survivors who were monitored for a mean of 11.6 years had chronic renal impairment, and five (63%) underwent urinary diversion/reconstruction procedures. The authors suggested that intervention may assist in getting the fetus to term, but that the sequelae of PUV may not be preventable by intrauterine intervention. Another, more recent series, reported that, although one third of survivors required dialysis and transplantation, the majority reported a reasonable quality of life.[180]

Vesico-amniotic shunting is notorious for complications. These occur in up to 45% of cases and include shunt blockage, shunt migration, preterm labor, urinary ascites, chorioamnionitis, and iatrogenic gastroschisis. Although the meta-analysis described 169 successful shunt placements, shunting was not technically possible or was associated with significant intraprocedural complications in another 15 cases.[176]

In the current climate, a suitable candidate for therapeutic intervention would be a fetus who has a normal male karyotype, sonographic features of lower urinary tract obstruction with or without oligohydramnios, absence of other fetal abnormalities that might adversely affect the prognosis and clinical outcome, good renal prognosis on fetal urine sampling, and fully informed and consenting parents. Correct case selection, long-term outcome, and the potential benefit of shunting are currently being evaluated within the Percutaneous Shunting for Lower Urinary Tract Obstruction (PLUTO) multicenter trial in order to comprehensively evaluate the role of this therapeutic intervention.

OPEN FETAL SURGERY

Harrison and colleagues reported the first successful in utero decompression for hydronephrosis with open fetal surgery in 1981.[181] Seven open fetal vesicostomies have also been reported, but half of the fetuses did not survive the neonatal period.[181-183] Because of the absence of obvious benefit in terms of outcome compared to shunting, as well as significant problems with preterm labor, premature rupture of the membranes, and fetal death, open fetal vesicostomy has been abandoned.

FETAL CYSTOSCOPY

Fetal cystoscopy has been introduced as an alternative to shunting as a therapeutic and diagnostic procedure. In utero percutaneous cystoscopy was first described by Quintero and colleagues[184] in the management of fetal obstructive uropathy under maternal general anesthesia[185] and more recently was reported by others using local anesthesia.[186] The indications are similar to those for vesico-amniotic shunting. Fetal hydrolaparoscopy and endoscopic cystotomy have also been reported.[187]

Fetal cystoscopy is performed by introducing a 14-gauge trocar and cannula through the maternal abdomen, uterus, and fetal abdomen into the fetal bladder under ultrasound guidance and antibiotic cover after local anesthetic infiltration.[186] Unlike the approach for shunting, the bladder needs to be approached from its superior aspect, so that the trocar can be aligned to enter in a straight line with the urethra. Color flow mapping is used to avoid the umbilical arteries. Urine is aspirated for repeat electrolyte sampling, and a detailed inspection is made of the bladder wall, especially for hemorrhage or trabeculation; ureteric orifices; entrance to the posterior urethra; hypertrophic muscle (if present) around the posterior urethra; and site and cause of obstruction if seen. Urethral valves, if visualized, are seen in the form of a membrane obstructing the urethral lumen that arises at the level of the verumontanum in the posterior urethra. Once the presence of PUV has been confirmed, various strategies may be applied in an attempt to treat it definitively, including pulsed-wave yttrium-aluminum-garnet (YAG) laser valve ablation[184]; pressure saline injection to disrupt the membranous valves, or, alternatively, insertion of a guidewire through the valves to mechanically disrupt them.[188]

OUTCOME OF FETAL CYSTOSCOPIC VALVE ABLATION

Quintero and colleagues[185] treated nine fetuses with lower urinary tract obstruction by fetal cystoscopy and laser ablation of the valves. Four of the nine fetuses did not have a patent urethra at birth (one had urethral atresia). Of the remaining five with a patent urethra, two were viable at birth, one had progressive renal damage and was aborted, and two were lost to chorioamnionitis. Of the two fetuses with patent urethras that survived the neonatal period, one had renal impairment and died at 4 months of age from bronchopneumonia, and the second died at 3 months from necrotizing enterocolitis. There were thus no survivors in this study, although this may have reflected the fact that entry was restricted to fetuses with poor prognostic factors.

Welsh and coworkers[188] undertook fetal cystoscopy on 11 fetuses between 16 and 24 weeks' gestation. There were no immediate or long-term iatrogenic complications from the procedure (such as membrane rupture, abruption, or preterm labor before 34 weeks). Five of the 11 cases were complicated by postprocedural urinary ascites, which was managed conservatively. Cystoscopy was performed for diagnosis in only seven cases. Among the remainder, therapeutic procedures were attempted in four cases with PUV (one with hydroablation and three with guidewire technique). The valves were completely destroyed in one fetus, a result that was confirmed radiologically as well as cystoscopically in the postnatal period. Two were judged to have partial success (increase in amniotic fluid volume and decrease in bilateral hydroureteronephrosis during pregnancy) but required treatment in the postnatal period. Three of the four had acceptable renal function in infancy.

The main challenge to fetal cystoscopy is technical difficulty, either in the ability to enter the posterior urethra with the cystoscope or in visualization of the valves. Further research and development are needed before this therapy can be more widely adopted.

DECISION MAKING IN THE ASSESSMENT OF THE ENLARGED BLADDER

The mortality and morbidity associated with the diagnosis of severe lower urinary tract obstruction in early gestation is high, and parents are often faced with a difficult decision whether to continue with the pregnancy. Assessment of the fetus should be undertaken in conjunction with advice from the pediatric urologists and nephrologists in order to inform parents as comprehensively as possible. Should termination be undertaken, or should the fetus die in utero or in the early postnatal period, postmortem analysis should be encouraged so that a precise diagnosis can be obtained to inform counseling and planning for any future pregnancy. The main challenges are defining the underlying pathology accurately before birth and identifying which fetuses may benefit from in utero intervention. Both severe and moderate prenatal lower outflow tract obstruction require further long-term outcome studies to define their implications for eventual renal function (Table 4-7).

Table 4-7 **Key Points for Assessment of the Enlarged Bladder**

What is the fetal sex?

Is there persistent dilatation?

Is the bladder tense or floppy?

Is the bladder wall thickened?

Is there a keyhole sign?

Assess renal tract for ureteric and renal pelvic dilatation

Assess the amniotic fluid volume

Look for extrarenal abnormalities

Consider karyotyping

Consider serial bladder aspiration and measurement of fetal urine for

- Sodium
- Calcium
- β_2-Microglobulin and new markers as they are recognized

Consider role of in utero shunting after all of the above have been carried out

Joint assessment with pediatric urologists and nephrologists

Postmortem examination in the event of termination of pregnancy or fetal demise

Long-term follow-up studies are required to fully evaluate the role of any in utero therapy

Absent Bladder

Persistent absence of the bladder should be considered as abnormal from 15 weeks' gestation. If the bladder is difficult to identify, color Doppler examination of the paravesical vessels should be undertaken, together with a detailed examination of the rest of the fetal anatomy. The causes of an absent bladder on fetal ultrasound can be divided into lack of fetal urine production or inability of the bladder to store urine.[189]

Lack of Fetal Urine Production

The finding of an absent bladder caused by a lack of fetal urine production is associated with oligohydramnios or anhydramnios and can be divided into prerenal and renal causes. Reduced urine production in the fetus may occur as a consequence of prerenal failure due to severe placental insufficiency. This results in generalized poor fetal growth in association with oligohydramnios and redistribution of blood flow within the fetus, with poor renal umbilical artery flow and an increase in flow to the brain, as evidenced by an increase in middle cerebral artery flow. In this situation, uterine artery Doppler values are usually abnormal. The finding of oligohydramnios and a poorly filled bladder with abnormal fetal and uterine artery Doppler results makes intrauterine growth retardation (IUGR) secondary to placental insufficiency the most likely etiology. Abnormal fetal biometry may also be present. Careful examination of the fetus should reveal the presence of normal kidneys; often, a small amount of fluid may be seen within the bladder.

Renal causes for lack of fetal urine production relate to bilateral pathologies: bilateral renal agenesis, in which there is no evidence of kidneys in the renal beds; bilateral MCDK, in which the dysplastic kidneys are nonfunctioning, have an atretic ureter, and consequently do not produce urine; and bilateral renal dysplasia. If both kidneys are dysplastic and have no function, absence of urine production will result in failure to visualize a fetal bladder in association with anhydramnios. As discussed earlier, absence of both kidneys or absence of any renal function will eventually be fatal.

Inability of Bladder Storage

If the volume of amniotic fluid is normal but the bladder cannot be visualized, then a urologic cause for the absent bladder should be sought. With normal urine production, an absent bladder indicates that either the urine is not reaching the bladder or the bladder is not able to store urine.

Bilateral Single Ectopic Ureters

Ectopic ureters are normally associated with a duplex system; however, rarely they can be identified in a single renal system. Unlike duplex kidney, this problem is more common in males. It is caused by an abnormality in ureteric bud development: the ureteric bud develops and enters the metanephric blastema medially. This results in the ureter's entering below the bladder neck in males, and in females it may even enter the genital tract. In addition, the abnormal interaction with the metanephric blastema often leads to the development of renal dysplasia. The urine therefore bypasses the urinary bladder, and if the problem is bilateral, the bladder may never fill. Consequently, these rare fetuses could present with an absent bladder but with normal amniotic fluid volume. However, accurate prenatal diagnosis of this condition is yet to be reported.

Table 4-8 Key Points on Identification of a Fetal Renal Tract Abnormality

Examine the whole renal tract, including objective measurement of amniotic fluid volume
Measure both kidneys and renal pelves in three dimensions to ascertain renal volume
Search for extrarenal abnormalities
Ascertain family history
Consider parental renal scans
Ascertain risks for aneuploidy and consider karyotyping
Refer to multidisciplinary clinic for counseling by pediatric nephrologists, urologists, geneticists
Consider the role of invasive assessment of renal function
Carry out a detailed postmortem examination in the event of termination, intrauterine demise, or neonatal death
Request retention of samples for future DNA analysis

CONCLUSION

Renal tract abnormalities are commonly found on prenatal ultrasound studies. Isolated abnormalities such as mild RPD often resolve during pregnancy or early neonatal life, and the potential benefit of detection in terms of monitoring progression and need for postnatal intervention should be balanced against the potential anxiety that is often induced in the parents on detection of an apparent abnormality. The identification of a renal tract abnormality should initiate a detailed examination of the remainder of the renal tract, to assess the likely effect on overall renal function both during gestation and after birth. In addition, the remainder of the fetal anatomy should be examined for other structural abnormalities and markers of aneuploidy. The results of any prior screening tests for Down syndrome should be taken into consideration, and enquiry about family history should be undertaken. It is not always possible to establish the specific underlying pathology during the pregnancy. Therefore, it is important in the event of fetal demise that a detailed postmortem examination be undertaken, together with retention of tissue or fluid for DNA analysis either then or in the future, so as to reach a specific diagnosis and thereby accurately inform the parents regarding risks to future pregnancies and to the wider family. Consideration should be given to parental and sibling renal scanning. In many cases, accurate prediction of outcome is not possible, and the establishment of multidisciplinary prenatal renal clinics—where parents can be seen and counseled by a fetal medicine specialist together with pediatric urologists, nephrologists, and, if appropriate, geneticists—can provide a joint approach to care and optimal counseling of parents both during the pregnancy and after delivery (Table 4-8).

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CHAPTER 5

MORPHOLOGIC STUDIES OF THE URINARY TRACT

J. Michael Zerin

Imaging plays a critical role in the evaluation of many disorders of the urinary tract in the infant and child. Advances in imaging technologies, as well as evolution in understanding of the pathophysiology of urologic diseases, both contribute to the continuing diversification in the imaging armamentarium, with the result that a varied array of imaging modalities is currently available for the investigation of urinary tract diseases. The purpose of this chapter is to provide an understanding of how these imaging studies are performed and the types of information that they provide which will help the reader to take full advantage of these very important diagnostic tools in evaluating patients in clinical practice.

ULTRASONOGRAPHY

Ultrasound (US) is the primary modality that is used for screening children with suspected urinary tract disease, and it has largely, if not completely, replaced the intravenous urogram (IVU). Dramatic growth in the use of US has in great measure resulted from the perception of US as a noninvasive, safe, and reliable screening modality requiring neither intravenous administration of contrast material nor exposure of the patient to ionizing radiation.[1,2] The absence of a need for shielding against ionizing radiation allows for a degree of portability that is unattainable with other imaging modalities. Affordability has also played an important role, given that even the most sophisticated US equipment is relatively inexpensive. Introduction of highly sophisticated, inexpensive, portable, laptop-based ultrasound units has promoted further expansion in the use of US. Continuing technologic innovation in transducer and software design, such as in tissue harmonic imaging, three-dimensional imaging, and the clinical application of sonographic contrast media, will continue to enhance the flexibility and ease of use of this modality, with associated improvements in image quality and diagnostic accuracy.

HOW ULTRASOUND WORKS: GRAY-SCALE AND DOPPLER TECHNIQUES

Two-Dimensional Gray-Scale Imaging

The contemporary US transducer alternately generates short pulses of sound and then listens for the returning echoes.[3] If the velocity of sound in tissue is assumed to be constant, the temporal delay between transmission of the insonating sound pulse and registration of the returning echoes is proportional to distance, allowing for spatial registration of the depth of the reflecting tissue interfaces. The amplitude of the returning signal is proportional to the reflectivity of the tissue. The two-dimensional gray-scale image is generated through spatial analysis of the temporal delay and amplitude information encoded in the returning echoes as they are detected across the entire surface of the transducer.

Duplex Doppler Imaging

The two-dimensional gray-scale images are produced using only the amplitudes of the reflected sound. However, the returning echoes also contain frequency and phase information. Because sound that is reflected by a moving target inside the patient, such as flowing blood or a jet of urine, experiences a change in frequency as it returns to the transducer, analysis of the direction and magnitude of the shift in frequency of the reflected sound echoes can also provide important information.[3-5] Analogous to the audible change in frequency of the train whistle as a locomotive first races toward and then away from the station, objects that are moving toward the transducer reflect sound at a higher frequency than that of the incident beam, whereas objects that are moving away reflect sound at a lower frequency. The magnitude of the Doppler frequency shift is proportional both to the speed of the object and the angle of insonation. There is no detectable Doppler frequency shift when the transducer is perpendicular to the direction of motion of the target. As the angle of insonation is decreased, the magnitude of the detectable frequency shift increases. For this reason, Doppler angles of less than 60 degrees are recommended for making velocity measurements. Temporal analysis of the Doppler shift at a selected location within a vessel is used to generate a waveform representation of the flow within the vessel throughout the cardiac cycle. Analysis of the shape of the waveform can be used to assess flow dynamics, including velocity, turbulence, and resistance. The combination of anatomic gray-scale US imaging with pulsed Doppler is referred to as duplex Doppler imaging.

Color Doppler Imaging

Color Doppler US analyzes phase, frequency, and amplitude information encoded in the returning echoes to overlay a color image displaying blood flow onto a real-time gray-scale image. Color is assigned to objects that are in motion (e.g., red blood cells in flowing blood) based on the direction of the phase shift. By convention, motion toward the transducer is encoded in red and motion away from the transducer in blue. Relative velocity (the Doppler frequency shift) is represented by the shade of red or blue, with faster flow assigned a lighter color and slower flow a darker color. The primary advantage of the color Doppler technique over pulsed Doppler is that it permits evaluation of a segment of a vessel or region of tissue, rather than being limited to a single point inside a vessel. However, because it relies on frequency information, color Doppler is limited by insensitivity to slow flow and insonating angle dependence.[3-5]

Power Doppler Imaging

Power Doppler US is a frequency-independent technique for assessing blood flow that estimates the integrated power or strength of the Doppler signal produced by a population of moving red blood cells within a vessel or region of tissue.

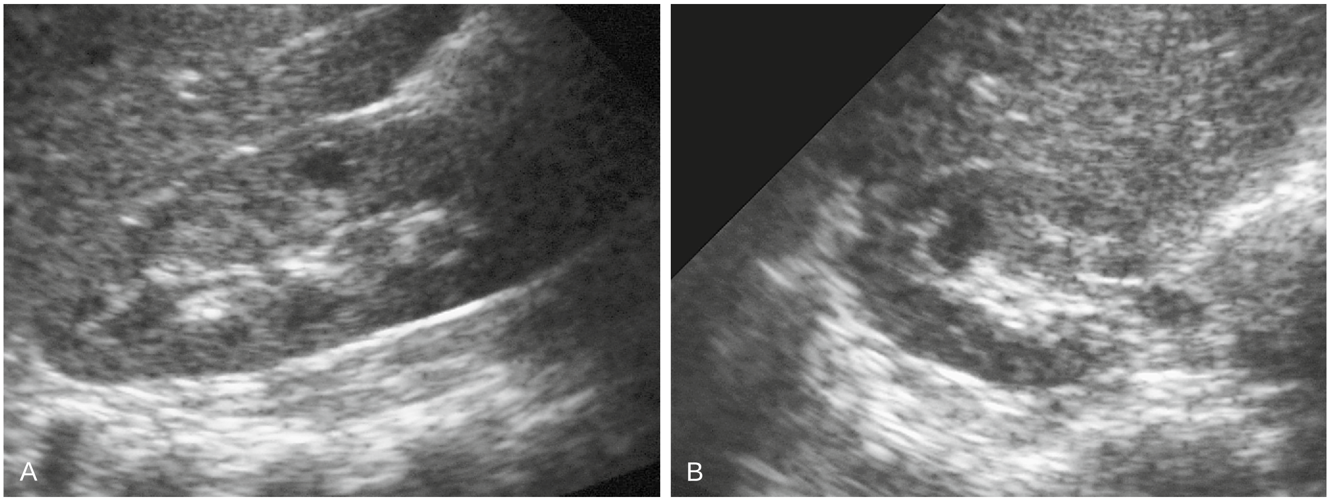


Figure 5-1 Normal gray-scale ultrasound image of the right kidney in a 5-year-old girl with previous urinary tract infections. Longitudinal coronal **(A)** and transverse **(B)** images of the right kidney show normal renal contours and parenchymal echogenicity. The prominently hypoechoic appearance of a medullary pyramid in the lower third of the kidney is a normal finding.

In power Doppler imaging, the intensity of the color signal corresponds to the total energy of the Doppler signal.[3,6] Because the frequency encoding is removed, power Doppler is more angle-independent than other Doppler techniques. Although intravascular microbubble contrast agents greatly increase the sensitivity of power Doppler to slow flow, they are not currently available clinically.

ULTRASOUND TECHNIQUE AND NORMAL APPEARANCES

Kidneys and Ureters

Sonographic imaging of the kidneys in transverse, coronal, and sagittal planes provides an excellent three-dimensional anatomic view of the renal parenchyma and collecting systems.[1,2] Because the kidneys are both more superficial and smaller in neonates and young infants than in older children and adults, higher-frequency transducers—typically 5 to 10 MHz—are needed to provide high-quality sonographic images. With the patient supine, the kidneys are interrogated in coronal and transverse planes with the transducer near or in the midaxillary line. From this vantage, the right kidney is imaged through the liver and the left kidney through the spleen. In the neonate and younger child, the longitudinal renal axes are roughly parallel to the spine. As the child grows into adolescence and adulthood, the sagittal and coronal renal axes gradually become more oblique as the psoas muscles enlarge and displace the lower poles anterolaterally. Both positional and pathologic curvatures of the spine in the coronal and sagittal planes can dramatically alter renal inclination and axis, requiring even the most skilled examiner to take a flexible approach to probe positioning and orientation. The left kidney is often more difficult to visualize in the coronal plane, because it lies closer to the diaphragm and is only incompletely covered by the spleen. This frequently allows bowel loops to become interposed between the transducer and the kidney, interfering with its interrogation. In older children, the kidneys often can be visualized to greater advantage during deep inspiration or when the patient increases the lumbar lordosis by pushing the stomach upward; however, these maneuvers require a cooperative patient and are not reproducible in neonates and young infants.

The kidneys can also be interrogated from a posterior, paraspinal projection with the patient prone. In this position, the transducer is placed lateral to the spine on each side of the midline and the kidneys are imaged in sagittal and transverse planes. Because the kidneys are more superficial and, therefore, much closer to the transducer when viewed from posteriorly than when they are interrogated in a coronal plane from the midaxillary line, it can sometimes be impossible to visualize either kidney in its entirety in longitudinal posterior projection using a sector transducer, because the width of the near field of view is too narrow. In this situation, a wide linear transducer can be helpful. Alternatively, a standoff gel-pad can be used to increase the distance between the transducer and the kidney.

Sonographically, the kidneys appear as roughly bean-shaped, solid, retroperitoneal organs lying along the upper, anterior surfaces of the psoas muscles on either side of the midline (Fig. 5-1). In cross section, the medullary pyramids appear as relatively hypoechoic, solid structures within the more hyperechoic renal cortex; they are radially arranged around the brightly echogenic renal sinus containing the renal collecting system, vessels, lymphatics, nerves, and fat. Because children generally have less fat than adults do, both within the renal sinus and around the kidney, the central echogenic renal sinus is less prominent early in life. On power Doppler imaging, the flow in the parenchyma is normally uniform diffusely throughout the kidney (Fig. 5-2).

In neonates and young infants, the medullary pyramids often appear strikingly hypoechoic.[1,2,7-9] Although medullary echogenicity gradually increases with age, the pyramids remain somewhat less echogenic than the renal cortex even in adults (see Fig. 5-1). In part, medullary hyperlucency is accentuated in very young patients by the increased cortical echogenicity that is also noted early in life. Whereas renal cortical echogenicity in older children and adults is normally less than that of the adjacent liver or spleen, the normal renal cortex in the neonate is frequently isoechoic, or even occasionally slightly more echogenic, than the other solid organs.[10,11] Physiologically increased neonatal renal cortical echogenicity has been attributed to a higher cortical glomerulotubular ratio early in life and typically disappears by 6 months of age. The medullary pyramids also frequently appear much larger in comparison with the overlying cortical mantle in neonates

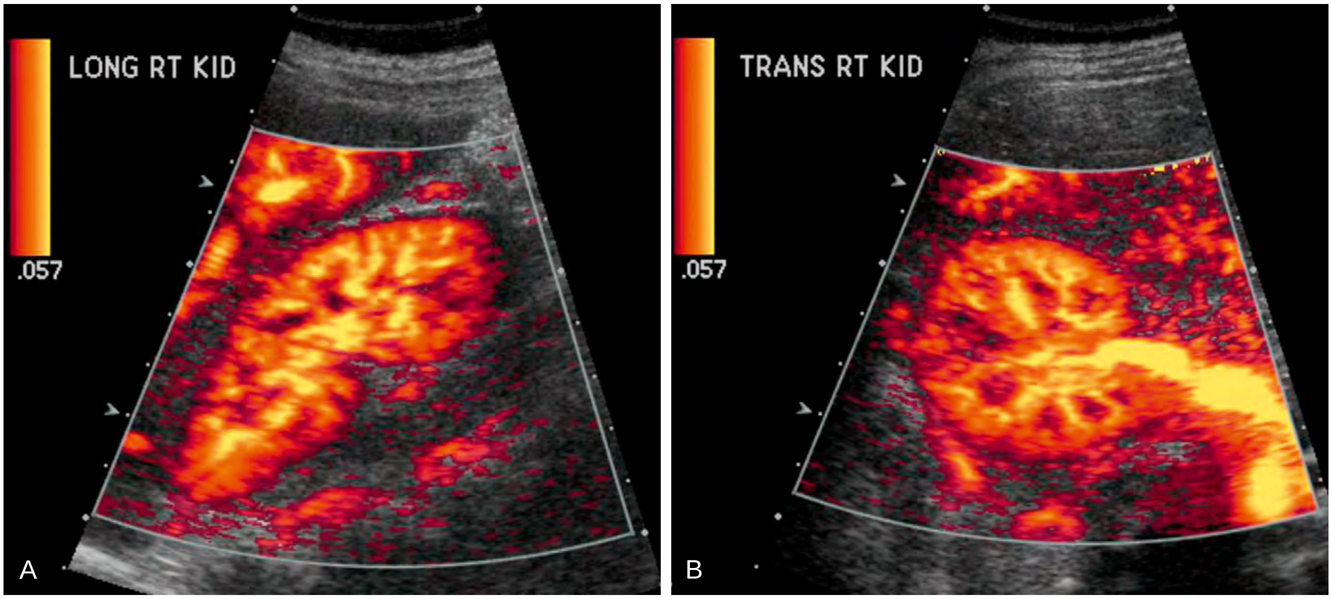


Figure 5-2 Normal power Doppler study of the right kidney in a 6-year-old girl with urinary tract infection. Longitudinal coronal view of the right kidney **(A)** and transverse image through the midpolar region of the right kidney **(B)** show perfusion diffusely throughout the kidney with no visible defects.

and infants, compared with older children and adults. The medullary rays are characteristically triangular or pyramidal in cross section, although compound pyramids in the renal poles can be quite large and irregular in contour. Familiarity with these normal differences in the sonographic appearance of the neonatal kidney is very important, because the less wary observer could occasionally mistake very hypoechoic medullary pyramids for dilated calyces or renal cysts. The absence of posterior acoustic enhancement and lack of dilatation of the renal pelvis and infundibula differentiate echolucent pyramids from hydronephrosis. Medullary pyramids are also generally more angular and irregular in shape than dilated calyces and cysts, which tend to be more smoothly rounded. Visualization of the echogenic margin of the arcuate artery at the outer perimeter of the papilla and the absence of any visible compression of the overlying cortex or distortion of the renal contour are additional clues to its normality.

Some normal variations in the contour of the neonatal and infant kidney occasionally cause confusion. Persistent fetal lobation is manifested by a smoothly undulating renal outline with superficial clefts between the incompletely fused fetal renal lobes. Although persistent fetal lobation is most commonly seen in neonates and young infants, this appearance can persist throughout life in some individuals and can be mistaken for renal masses or cortical scarring.[12] In fetal lobation, the clefts characteristically lie between the medullary pyramids, rather than overlying them as in reflux nephropathy, and the echo texture of the underlying renal parenchyma is normal. The junctional parenchymal defect appears as a triangular, echogenic, cortical indentation along the anterolateral aspect of the junction of the middle and upper thirds of the kidney.[13] The defect extends inferomedially for a variable distance into the renal sinus and represents the anterior site of fusion of the superior and inferior renunculi, the two primitive nephrogenic masses that combine to form the kidney. Differentiation from a cortical scar or peripheral echogenic tumor is based on the triangular shape of the defect and its characteristic location. Prominent cortical infolding occurring at the interfaces between the renal lobes is referred to columns of Bertin and is most commonly visible on transverse images through the midsections of the kidneys; it should not be mistaken for an area of parenchymal edema or a renal mass.

Visualization of a small amount of urine separating the walls of the collecting system in the renal sinus is a frequent sonographic observation in neonates and young infants.[1,2,7,8,14,15] Whereas such "dilatation" of the renal pelvis would generally be considered to be abnormal in an older child or adult, the situation is quite different in neonates and young infants. In the absence of infundibular or calyceal dilatation, isolated mild distention of the renal pelvis, so-called pelviectasis, is rarely progressive. This appearance in a neonate or young infant is probably physiologic in most cases and is related to the highly compliant nature of the renal collecting system in this age group.[7,8,14-16] If the renal pelvis is "extrarenal," the dilatation can be even more pronounced. Acute or chronic distention of the urinary bladder can augment such physiologic pelviectasis. Concurrent diuresis can further augment the dilatation.[17,18] Therefore, US examinations that are performed after diuretic renal scintiscans—or, in the past, after IVU with ionic contrast media—may show greater distention of the renal pelvis than do scans performed before these procedures. If upper tract dilatation is secondary to bladder distention, catheterization of the urinary bladder and complete decompression of the lower urinary tract—by aspiration of the bladder urine into a syringe, if necessary—can lead to rapid improvement in the appearance of the kidneys. If the ureters and collecting systems are severely distended, the bladder will again become distended as urine drains into it from above. In this situation, it may be necessary to repeat the aspiration of the bladder contents in order to decompress the entire urinary tract.

There is no single measurement that can be used reliably as a threshold value to differentiate physiologic renal pelvic distention from mild obstructive hydronephrosis that will progress in the future. It is widely accepted, however, that assessment of the anteroposterior dimension of the renal pelvis, as visualized on transverse views through the renal hilum, is much more useful than measurements of renal pelvic size in the coronal or sagittal planes. Frequently, although the coronal or sagittal dimensions of the renal pelvis appear quite large on longitudinal scans, the pelvis appears very shallow or even not identifiable on transverse images through the renal hilum. Whenever the “renal pelvis” appears to be mildly distended only on a single projection, it is important to consider the possibility that normal vessels in the renal hilum are being confused for a distended renal pelvis. In this regard, Scola and colleagues[19] showed, using Doppler US, that more than 60% of cases initially interpreted based on conventional gray-scale images as representing mild “hydronephrosis” actually involved vessels coursing in the renal sinus rather than a dilated renal pelvis.

The importance of accurate and precise evaluation of renal size and the rate of renal growth in infants and children who undergo imaging studies because of suspected urinary tract disease has been repeatedly emphasized in the literature. Sonographic and urographic standards have been published for the comparison of measurements of renal length or volume with age as well as with a variety of morphometric parameters such as height, weight, and body surface area.[20-23] Although the rate of renal growth roughly parallels both age and general somatic growth throughout childhood, this statement greatly oversimplifies what is actually a very dynamic relationship.[24-26] At birth, the maximum renal dimension is less than half what it will be at maturity, and renal weight and volume are only one-tenth as much in the adult. Renal growth is most rapid during the first weeks of life, with the renal length measured by US increasing as much as 15% to 20% in full-term neonates during this brief period alone.[20-22,24-26] The rate of renal growth then slows gradually. Between 2 and 10 years of age, the rate of increase in renal length stabilizes at approximately 2 to 3 mm/yr; it then declines again in the preadolescent and adolescent years, until it ceases at maturity.

Demonstration that the renal lengths are “normal” at the time of a single examination does not necessarily guarantee either that the kidneys have been growing normally or that they will continue to do so in the future.[24,26-30] Conversely, documentation that a kidney is abnormally small or large in comparison with a particular set of normative standards on a single examination does not necessarily imply that that kidney is currently growing at an abnormal rate. Comparison of multiple measurements obtained on successive imaging studies and represented on a renal growth chart is the most accurate method for assessing the pattern of renal growth.[20,21,27,28] The left kidney is often slightly longer and larger in volume than the right; however, the difference in renal size between the two sides is small and inconsistent. Renal sizes that are reproducibly asymmetric or that fall outside the normal range should be suspect, particularly if serial examinations fail to document an appropriate rate of growth. Although the renal measurements can vary with the patient in different positions, the location and transducer angle from which the longest renal axis can be obtained are routinely influenced by factors over which the examiner has little or no control, including interference by intestinal gas and overlying dressings, tubes, wounds, and scars; abnormalities in the positions and axes of the kidneys; and spinal deformities. Patient hydration can also affect sonographic renal size, as can administration of diuretic medications or intravenous contrast material.

The clinical relevance of the assessment of renal size and rate of renal growth is underscored by the potential diagnostic and prognostic implications of sonographic demonstration of nephromegaly or an abnormal acceleration in the rate of renal growth, or both, as signs of compensatory renal hypertrophy. Renewed interest in the frequency and timing of compensatory hypertrophy in neonates who are born with solitary functioning kidneys, for example, has been stimulated by the window provided by antenatal US. Sonographic evidence of compensatory renal hypertrophy has conventionally been assumed to be a desirable finding in patients who have solitary functioning kidneys—whether congenital or consequent to unilateral nephrectomy. Demonstration that the absence of nephromegaly in neonates who were born with multicystic dysplastic kidney is correlated with the presence of other urologic abnormalities (e.g., vesicoureteral reflux) offers some support for this concept.[30] Along related lines, Koff and associates[31] suggested that sonographic evidence of hypertrophy of the contralateral, normal-appearing kidney in neonates who are born with unilateral hydronephrosis and have indeterminate findings at diuretic renography might have prognostic significance in predicting the future risk for worsening obstruction and functional deterioration in the dilated kidney. DeBaun and colleagues[32,33] presented evidence that the risk of Wilms’ tumor in children with Beckwith-Wiedemann syndrome might be correlated with renal size. Their findings, if confirmed, suggest that ongoing sonographic surveillance for tumor development might be unnecessary in some children who do not have nephromegaly.

Nondilated ureters of normal caliber are not identifiable on US.[1,2] Mildly distended segments of the ureters can occasionally be visualized transiently as a bolus of urine is conveyed downward to the bladder, but this does not necessarily imply either obstruction or reflux. Moreover, the ureters can be mildly distended in a normal child who has a very full bladder and in a child who is undergoing diuresis from any cause.

BLADDER

Careful examination of the distended urinary bladder is an essential part of any sonographic study of the urinary tract in a child of any age (Fig. 5-3).[1,2] In neonates and infants, and in older children who are incontinent, the bladder should be interrogated first, to avoid the possibility that the child might empty the bladder while the kidneys are being examined. If the bladder is empty at this time, it can be re-evaluated after the kidneys have been imaged, at which point it will usually be more distended. In children who are potty-trained, the bladder can be routinely evaluated at the end of the examination, when it will be maximally distended. In some cases, catheterization and infusion of sterile saline or contrast material may be necessary to provide sufficient distention of the urinary bladder to allow a satisfactory examination. In the transverse plane, the normal bladder is rhomboidal in shape, and its distended wall is thin and smooth.[34] Longitudinally, the bladder appears more ovoid, with its apex anteriorly and its base along the pelvic floor posteriorly.

The bladder wall normally has a smooth contour and measures up to 3 mm in thickness when the bladder is well distended.[34] The bladder wall often appears somewhat thicker and may appear mildly irregular if the bladder is not well distended. Diffuse thickening of the bladder wall frequently evokes the possibility of bladder outlet or urethral obstruction or neurogenic dysfunction.[35] However, it is also seen in children with recent or recurrent urinary infection and in those with dysfunctional voiding. In cystitis, the thickening is caused by inflammatory infiltration and edema of the bladder wall (Fig. 5-4). The bladder may also be more echogenic than normal, with increased flow to the bladder wall and perivesical tissues visible on Doppler imaging. Common causes of focal thickening of the bladder wall include focal bacterial or viral cystitis, collapsed ureterocele, and postoperative thickening. Nodular thickening at the site of ureteral

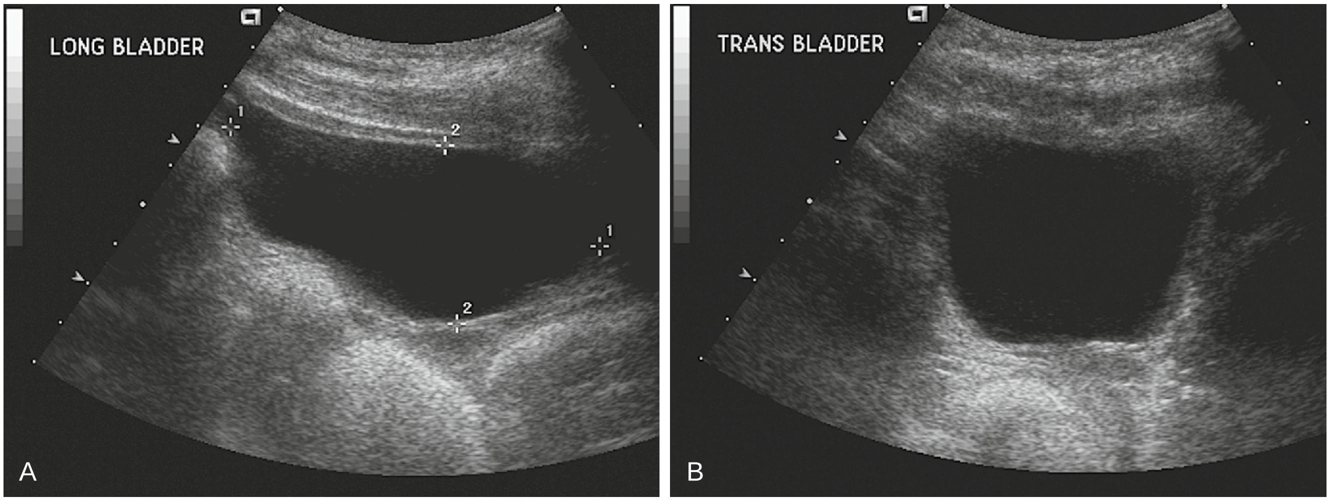
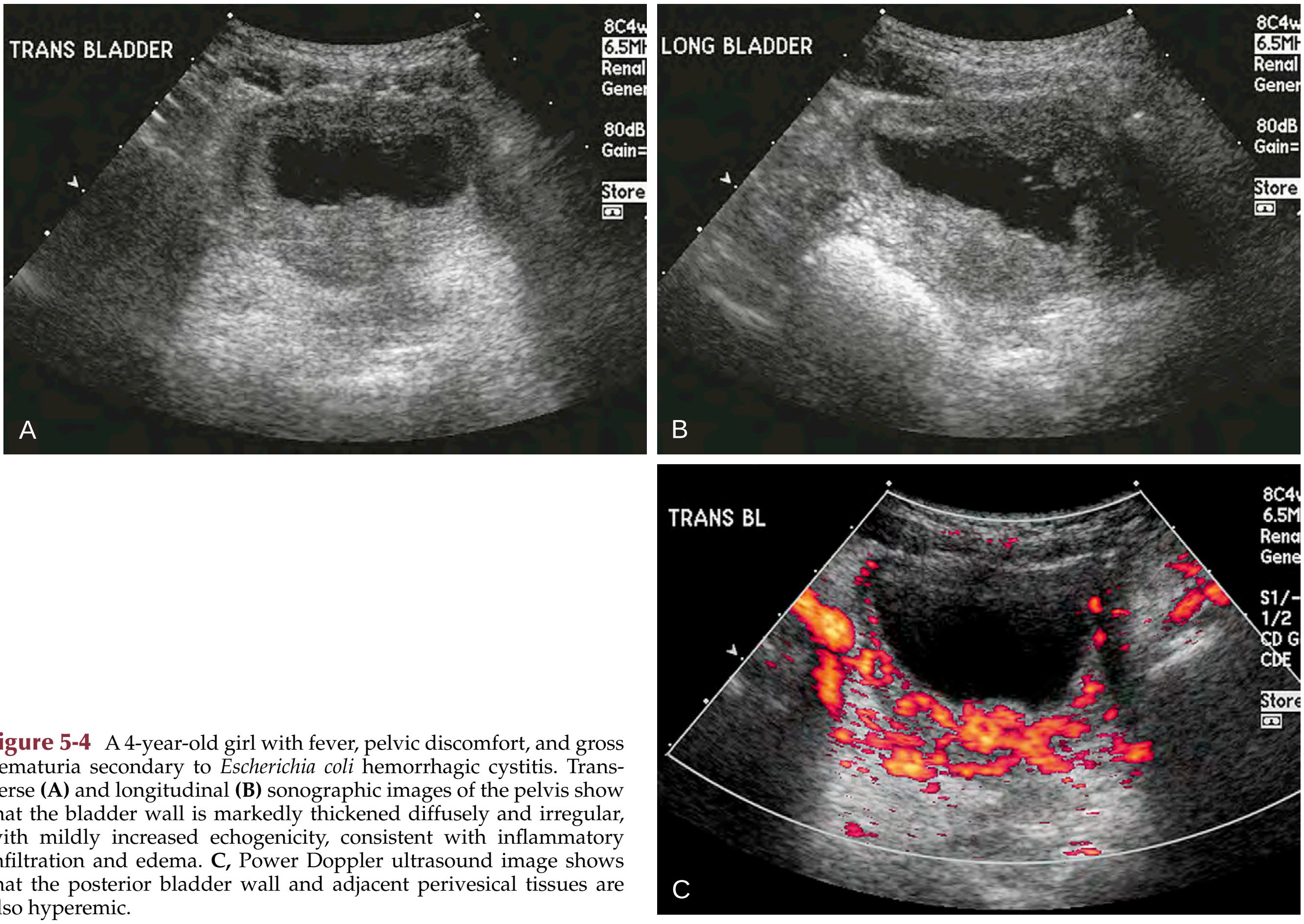

LONG BLADDER
1
2
1
2
A
TRANS BLADDER
B

Figure 5-3 Normal gray-scale ultrasound image of the urinary bladder in a 5-year-old girl with previous bilateral vesicoureteral reflux. Midline longitudinal **(A)** and transverse **(B)** views of the distended urinary bladder demonstrate the normal rhomboidal shape of the bladder, which is filled with anechoic urine and has a smooth and uniformly thin wall.


TRANS BLADDER
8C4w
6.5MH
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LONG BLADDER
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80dB
Gain=
Store
B
TRANS BL
8C4
6.5M
Rena
Gene
S1/-
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CD G
CDE
Store
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Figure 5-4 A 4-year-old girl with fever, pelvic discomfort, and gross hematuria secondary to *Escherichia coli* hemorrhagic cystitis. Transverse **(A)** and longitudinal **(B)** sonographic images of the pelvis show that the bladder wall is markedly thickened diffusely and irregular, with mildly increased echogenicity, consistent with inflammatory infiltration and edema. **C,** Power Doppler ultrasound image shows that the posterior bladder wall and adjacent perivesical tissues are also hyperemic.

reimplantation can mimic a polypoid mass. The echogenic nodule that is produced after periureteral Deflux injection can have a similar appearance; visualization of the ureteral jet arising from the Deflux mound confirms the proximity of the mound to the ureteral orifice (Fig. 5-5).[36] The cause of the thickening is usually suggested by the clinical presentation of the patient. Rarely, children with severe cystitis present with dramatic nodular bladder wall thickening which, if focal or disproportionately severe along the bladder base, can be mistaken for neoplasm.[37]

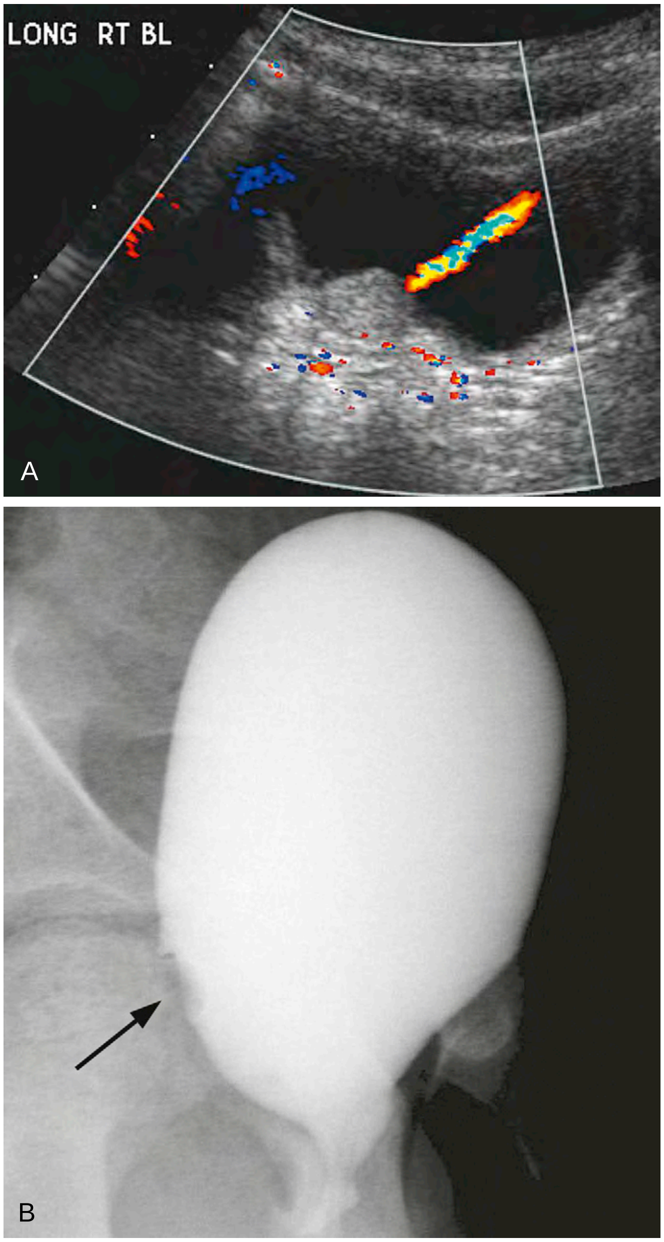

Figure 5-5 Sonographic evaluation of the bladder after right Deflux injection in a 5-year-old girl with previous right vesicoureteral reflux. **A,** Transverse duplex Doppler ultrasound image of the bladder shows the echogenic Deflux mound on the right side of the bladder base, with the ureteral jet issuing from the top of the mound, confirming the proximity of the mound to the ureteral orifice. **B,** Steep left posterior oblique view of the same bladder on a voiding cystourethrogram performed the same day shows the filling defect caused by the Deflux mound *(arrow)*.

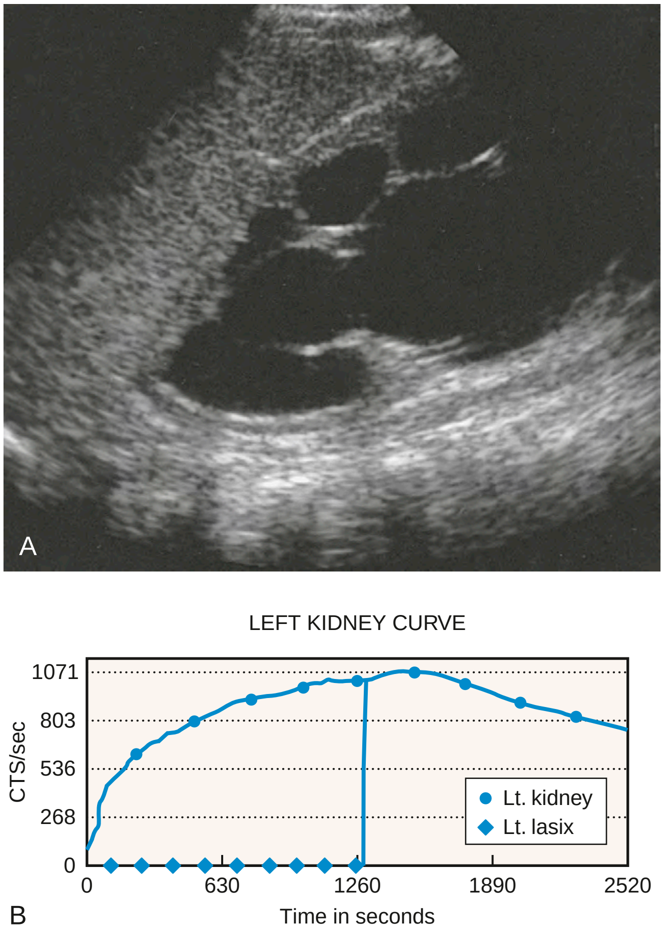

Figure 5-6 Severe hydronephrosis and cortical thinning secondary to intrinsic ureteropelvic junction stenosis in a 4-month-old boy with antenatally detected hydronephrosis. **A,** Longitudinal sonographic view of the left kidney. There is severe (grade IV) hydronephrosis. The parenchyma is thinned and diffusely echogenic with no identifiable corticomedullary differentiation, consistent with dysplasia. **B,** Technetium 99m MAG3 diuretic renal scan, showing washout curve for the left kidney. There is abnormally prolonged retention of the radiopharmaceutical in the left kidney after administration of diuretic, consistent with obstruction.

INDICATIONS FOR ULTRASOUND IN THE PEDIATRIC URINARY TRACT

Urinary tract infection and toileting dysfunction remain the most common indications for renal sonography in children.[1,2] However, neonates represent the most rapidly growing population of new patients who are referred for pediatric uroradiologic evaluation. Hydronephrosis (Fig. 5-6) is the most common fetal structural abnormality that is discovered during antenatal US performed after the 15th to 16th gestational week.[7,8] US is used to diagnose and characterize almost all common structural abnormalities of the upper urinary tract in neonates and children, such as multicystic dysplastic kidney (Fig. 5-7), renal dysplasia (Fig. 5-8), renal agenesis (Fig. 5-9) and ectopia, and complicated renal duplication anomalies (Fig. 5-10), and for monitoring the severity of hydronephrosis over time. It is also invaluable for monitoring renal growth in children who have urinary tract infection or vesicoureteral reflux, or both. US is also used for urologic surveillance in children with neurogenic bladder dysfunction and for postoperative evaluation in children after surgical procedures on the upper and lower urinary tract.

Awareness of the potential for occult renal disease has led to a dramatic increase in renal sonographic screening.[1,2] This includes neonates and infants who have nongenitourinary anomalies or syndromes that are associated with renal abnormalities, such as esophageal atresia, vertebral segmentation anomalies, or imperforate anus, as well as those who have abnormalities of the external genitalia (e.g., cryptorchidism, hypospadias). Sonographic screening is also performed routinely in neonates and infants

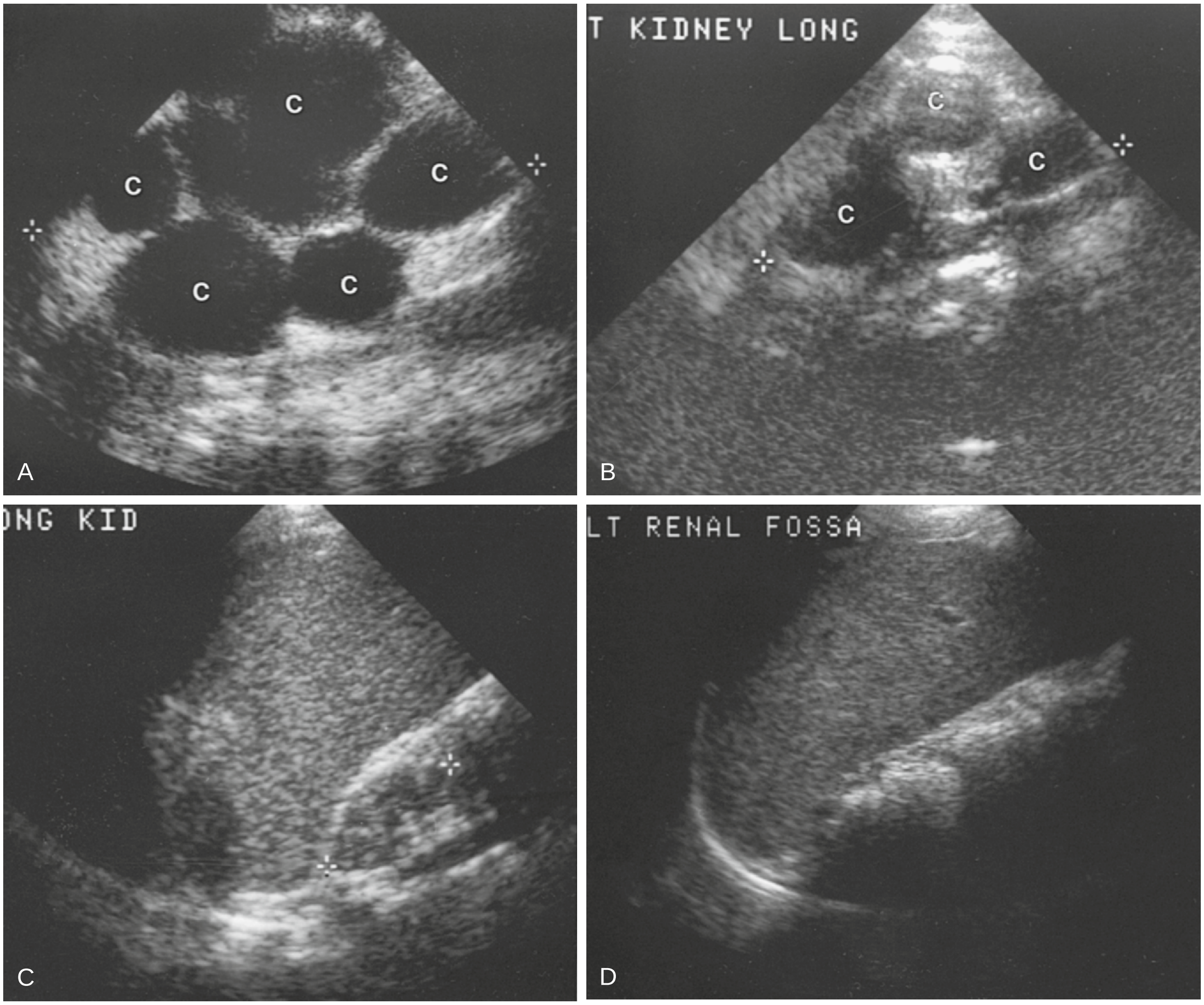

Figure 5-7 Classic multicystic dysplastic kidney with progressive involution (longitudinal sonographic images). **A,** View of the left kidney on the second day of life. The kidney measures 7.6 cm and is entirely replaced by noncommunicating cysts (C) of various sizes. The cysts are separated by thin strands of dysplastic, echogenic parenchyma. No normal parenchyma is visible. **B,** The left kidney of the same patient at 6 months of age. The multicystic kidney measures 5.6 cm in length. Three small cysts (C) and some echogenic dysplastic parenchyma are still visible. **C,** The left kidney at 21 months of age. The kidney measures 2.4 cm in length. No cysts are visible. **D,** The left renal fossa at 9 years of age. The left kidney is no longer identifiable.

who have anomalies or syndromes that present an increased risk for renal malignancy, such as Beckwith-Wiedemann syndrome, aniridia (Fig. 5-11), and hemihypertrophy.[33,38] Recognition of the importance of genetic factors in the transmission of common forms of congenital uropathology has similarly resulted in widening acceptance of the need for routine screening of asymptomatic siblings of infants and children who are known to have vesicoureteral reflux, as well as the newborn offspring of adults who themselves had reflux as children.[39-41]

RADIOGRAPHIC AND FLUOROSCOPIC MODALITIES

Abdominal Radiography

A plain radiograph of the abdomen and pelvis can reveal important clues regarding the presence and nature of urinary tract disease in infants and children. The lumbosacral spine, hips, and soft tissues should be carefully inspected for any evidence of an underlying neuromuscular disorder or anomaly that might be associated with neurogenic bladder dysfunction. Similarly, the bowel gas pattern may yield important information in regard to constipation, whether functional or neuropathic. Displacement of the bowel loops can be an important clue to the presence of a renal or retroperitoneal mass. Vertebral segmentation anomalies (Fig. 5-12) are frequently associated with renal anomalies, particularly renal agenesis, renal ectopia, and multicystic dysplastic kidney, and anomalies of the sacrum are more specifically associated with anorectal malformations. Widening of the pubic symphysis is almost always present in children with the epispadias-exstrophy complex and cloacal anomalies. The radiographic conspicuity of renal, ureteral, and bladder calculi (Fig. 5-13) varies greatly depending on the composition of the stones, their size and location, and interference of overlying structures with their visualization.

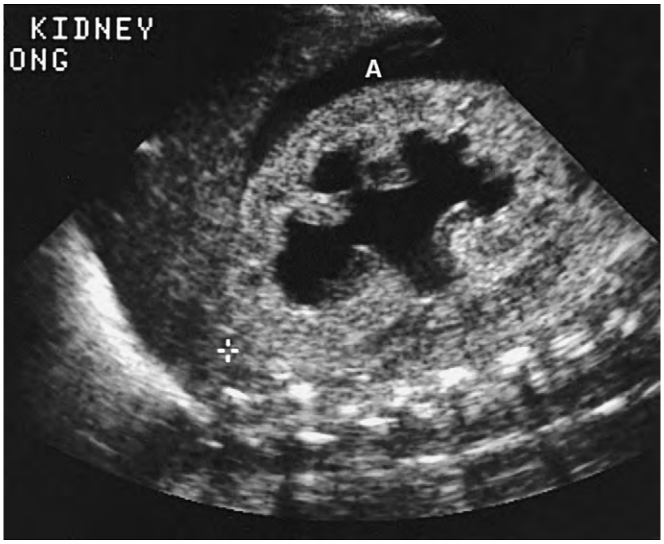

Figure 5-8 Right "microcystic" renal dysplasia in a premature neonate (estimated gestational age, 28 weeks) with very poor renal function. Longitudinal sonographic view of the right kidney on the first day of life. The parenchyma of the kidney is diffusely echogenic with no corticomedullary differentiation. The collecting system is dilated and somewhat dysmorphic in shape. Ascites (A) is visible anterior to the kidney in Morison pouch.

Intravenous Urography

IVU has been all but replaced in pediatric imaging by other modalities, including US, renal scintigraphy, computed tomography (CT), and magnetic resonance urography, with few indications for the examination remaining. In fact, because of the widespread availability of CT, few pediatric radiology departments in the United States have even retained the ability to perform linear tomography. As a result, even if IVU is to be done, its performance is usually limited to a series of plain radiographs alone. In our own department, we perform at most two to three IVUs a year, in each case at the insistence of the referring physician and despite our own recommendation that another modality be performed in its place. Nonetheless, images simulating those obtained with the conventional IVU are at times obtained after administration of intravenous iodinated contrast media for other examinations (e.g., computed tomography, abdominal or cardiac angiography). Although the diagnostic value of such images may be more limited than with formal IVU, the principles of interpretation are the same.[42]

The minimum approach to the pediatric IVU includes a scout view of the abdomen and pelvis before contrast material is administered and two anteroposterior radiographs of the abdomen and pelvis at 5 and 10 minutes. Additional oblique or lateral views and delayed images can be obtained as required. Serious allergic and other adverse reactions to intravenous contrast media are relatively rare in children, particularly when non-ionic, low-osmolarity urographic contrast media are used.[43] Appropriate preparation of the patient for the examination by fasting is important, both to improve visualization of contrast material in the kidneys and ureters and to reduce the frequency and severity of contrast-induced nausea and vomiting.

Voiding Cystourethrography

The fluoroscopic voiding cystourethrogram (VCUG) is the most reliable examination for diagnosing and characterizing vesicoureteral reflux in children.[44,45] It also provides excellent anatomic and functional information regarding the bladder, bladder neck, and urethra. However, the need for bladder catheterization often provokes considerable anxiety. Although parents occasionally request that their child be sedated for catheterization, this is rarely necessary. Short-acting agents such as midazolam have been used successfully in some centers and do not affect the results of the examination.[46,47] However, because the child needs to be awake during the examination, formal procedural sedation and anesthesia are not used, except in exceptional circumstances. Despite the discomfort that is associated with catheterization, most children will cooperate if the examiner speaks directly to the child supportively and explains what is to be done. The involvement of a child life specialist before and during the catheterization can also be beneficial.[48] Parents should be encouraged to remain with their child whenever possible. This may also help to reduce future anxiety in children who will return for follow-up studies and in those whose siblings may also be referred for evaluation. Although previous unpleasant experiences with catheterization or cystography can reduce patient cooperation, excessive anxiety on the part of the child or parent, or both, may suggest significant disturbance in family dynamics or, rarely, the possibility of sexual abuse.

The technique of bladder catheterization for VCUG in children has been described in detail in the pediatric imaging literature.[49] A disposable, 8F (2.64 mm), non-latex[50,51] catheter with a single end-hole can be used in most patients, although a smaller catheter may be necessary in neonates and infants. Other specialized catheters, such as coudé catheters, can be very useful in children with complex urethral abnormalities and in those with urogenital sinus and cloacal anomalies. However, catheters larger than 8F and balloon catheters are unnecessary. Children who are on a self-catheterization program should insert the catheter themselves, or their parent can insert the catheter if the child is too young or is developmentally challenged. This affords an opportunity to directly observe any difficulties they may be having during catheterization.

Cystographic Contrast Media and Bladder Filling

Cystographic water-soluble contrast media with iodine concentration between 15% and 20% (wt/vol) should be used.[44,52-54] More dilute media have insufficient radiopacity and should not be used. Conversely, contrast media with more than 25% iodine (wt/vol) and ionic intravenous media are very irritating to the bladder and urethra.

Infusion of the contrast material by gravity drip with the bottle hung from an IV pole is the most convenient method for filling the child's bladder during cystography. The contrast material can also be gently infused into the bladder by hand from a syringe, although this is impractical for completely filling the bladder except in neonates. Because intravesical pressure equilibrates with the hydrostatic pressure in the reservoir and tubing at capacity, the bottle should be hung no more than 60 to 70 cm above the tabletop, to avoid overdistending the bladder.[55] Overdistention of the bladder is particularly to be avoided in the child who has had previous bladder surgery, especially bladder augmentation, or who performs intermittent self-catheterization because of the risk of bladder perforation.[56]

The child's bladder should be filled completely, both to provide a reliable estimate of functional bladder capacity and to ensure that reflux occurring only near capacity or during voiding will not be missed. Bladder capacity can be roughly estimated[57] using the following formula:

$$\text{Bladder capacity} = (\text{Age in years} + 2) \times 30\ \text{mL}$$

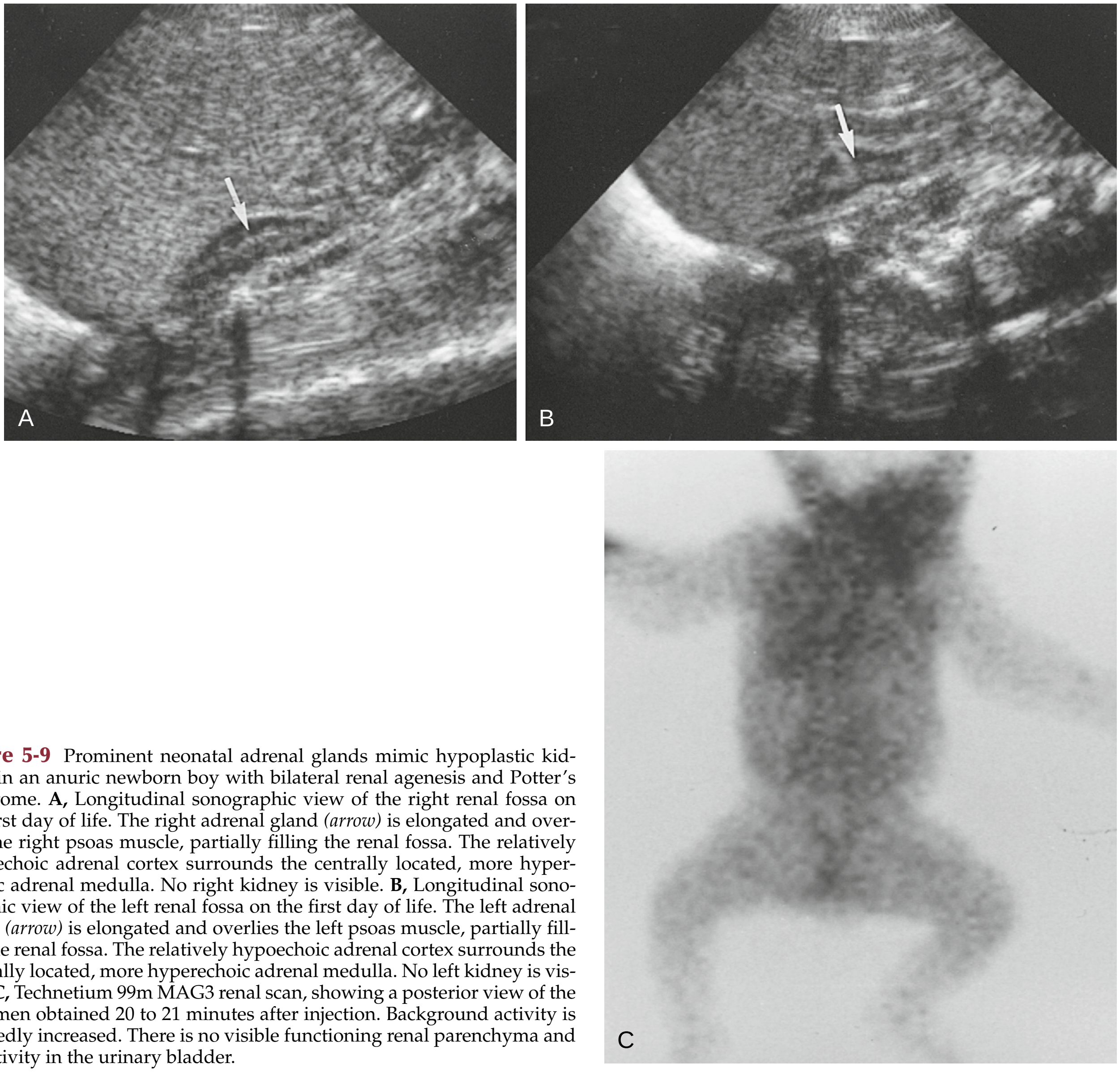

Figure 5-9 Prominent neonatal adrenal glands mimic hypoplastic kidneys in an anuric newborn boy with bilateral renal agenesis and Potter's syndrome. **A,** Longitudinal sonographic view of the right renal fossa on the first day of life. The right adrenal gland *(arrow)* is elongated and overlies the right psoas muscle, partially filling the renal fossa. The relatively hypoechoic adrenal cortex surrounds the centrally located, more hyperechoic adrenal medulla. No right kidney is visible. **B,** Longitudinal sonographic view of the left renal fossa on the first day of life. The left adrenal gland *(arrow)* is elongated and overlies the left psoas muscle, partially filling the renal fossa. The relatively hypoechoic adrenal cortex surrounds the centrally located, more hyperechoic adrenal medulla. No left kidney is visible. **C,** Technetium 99m MAG3 renal scan, showing a posterior view of the abdomen obtained 20 to 21 minutes after injection. Background activity is markedly increased. There is no visible functioning renal parenchyma and no activity in the urinary bladder.

However, individual differences in fluid intake and frequency of micturition produce wide variation in bladder capacity, even among healthy children of similar ages.[58] From a practical point of view, bladder capacity during cystography can be defined as the intravesical volume at which either the child voids spontaneously (or leaks if incontinent) or the flow of contrast material ceases while the child is quiet. Children frequently complain of being "full" at infused volumes far less than their true capacity, even though they may not be able to initiate micturition until a considerably greater volume is infused. When the child is crying or straining, the contrast material may stop flowing temporarily because of elevation in the intra-abdominal pressure. Early interruption of the infusion in such cases would result in underestimation of the true capacity and would decrease the likelihood that the child would be able to void on the fluoroscopy table.

A single cycle of bladder filling and emptying is sufficient in most children. However, if reflux is strongly suspected but is not demonstrated on the first cycle, performing a cyclic study in which the bladder is filled multiple times may increase the sensitivity of the examination for occult reflux.[59,60] This technique is also particularly useful in documenting small amounts of reflux into urethral ectopic ureters in girls with incontinence.[61] It can also aid in demonstrating reflux into markedly dilated ureters, in which the refluxed contrast material is diluted and therefore more difficult to see.

Getting the Child to Void

In the neonate and young infant, micturition is initiated on a reflex basis in response to bladder distention.[58] If emptying is incomplete, dribbling tepid water from a syringe onto the infant's perineum or feet or feeding the child often can induce further emptying. During the second and third years of life, children may be aware of bladder distention and fullness, and by 4 to 5 years they may even become able to communicate that micturition is imminent. However, many are still unable to initiate voiding voluntarily on command. Rapid

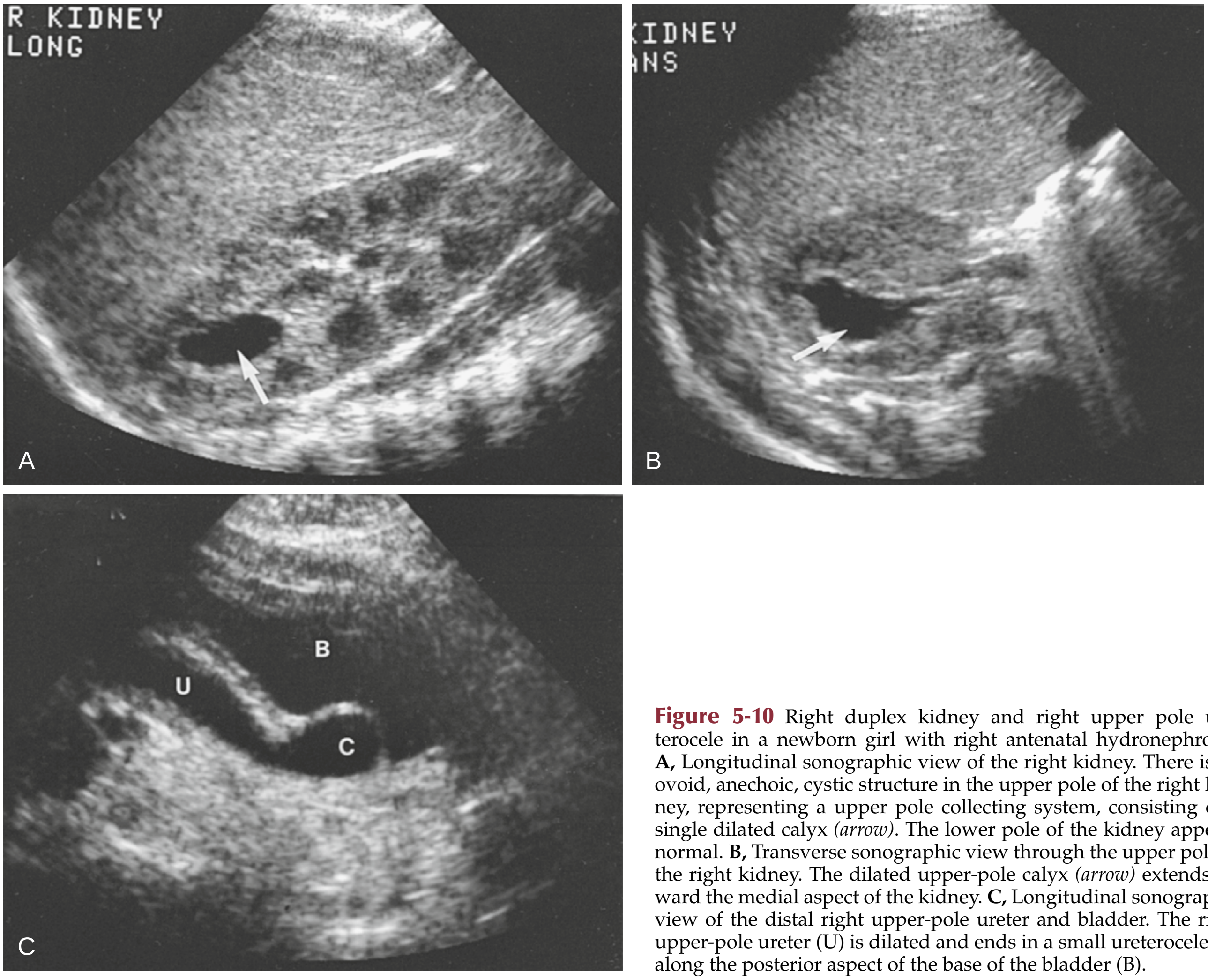

Figure 5-10 Right duplex kidney and right upper pole ureterocele in a newborn girl with right antenatal hydronephrosis. **A,** Longitudinal sonographic view of the right kidney. There is an ovoid, anechoic, cystic structure in the upper pole of the right kidney, representing a upper pole collecting system, consisting of a single dilated calyx *(arrow)*. The lower pole of the kidney appears normal. **B,** Transverse sonographic view through the upper pole of the right kidney. The dilated upper-pole calyx *(arrow)* extends toward the medial aspect of the kidney. **C,** Longitudinal sonographic view of the distal right upper-pole ureter and bladder. The right upper-pole ureter (U) is dilated and ends in a small ureterocele (C) along the posterior aspect of the base of the bladder (B).

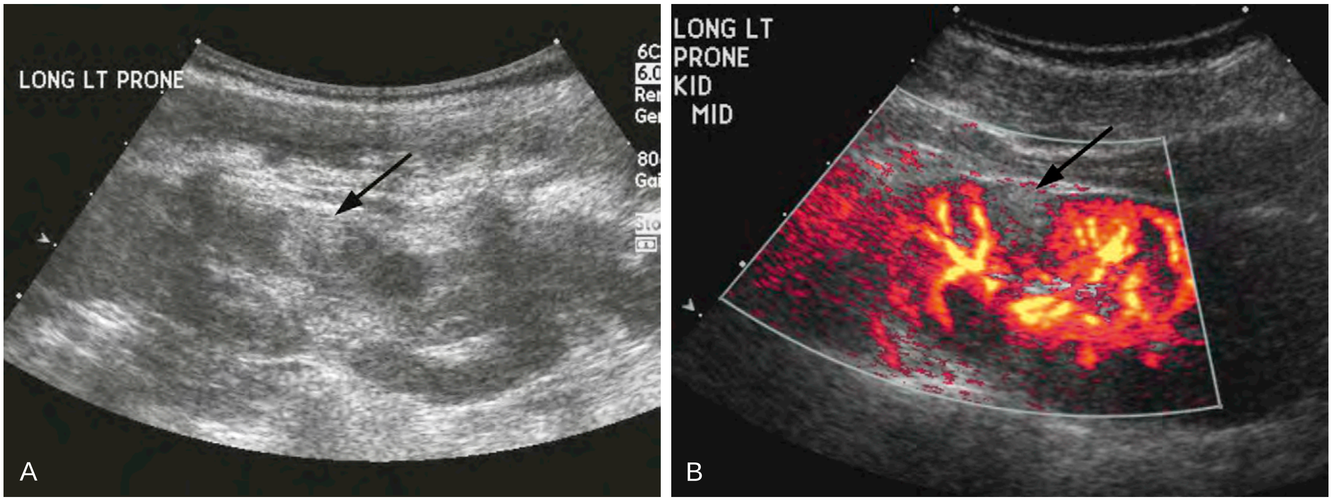

Figure 5-11 Use of power Doppler ultrasound in the identification of a small Wilms' tumor in a 2-year-old girl with sporadic aniridia. **A,** Longitudinal posterior gray-scale ultrasound image of the left kidney with the patient prone shows a subtle echogenic lesion *(arrow)* in the posterior cortex of the interpolar region of the kidney which does not appear to alter the renal contour. **B,** Longitudinal posterior power Doppler image of the left kidney confirms the presence of the lesion in the posterior interpolar region of the kidney and more clearly delineates its margins and size based on the distortion of the parenchymal flow.

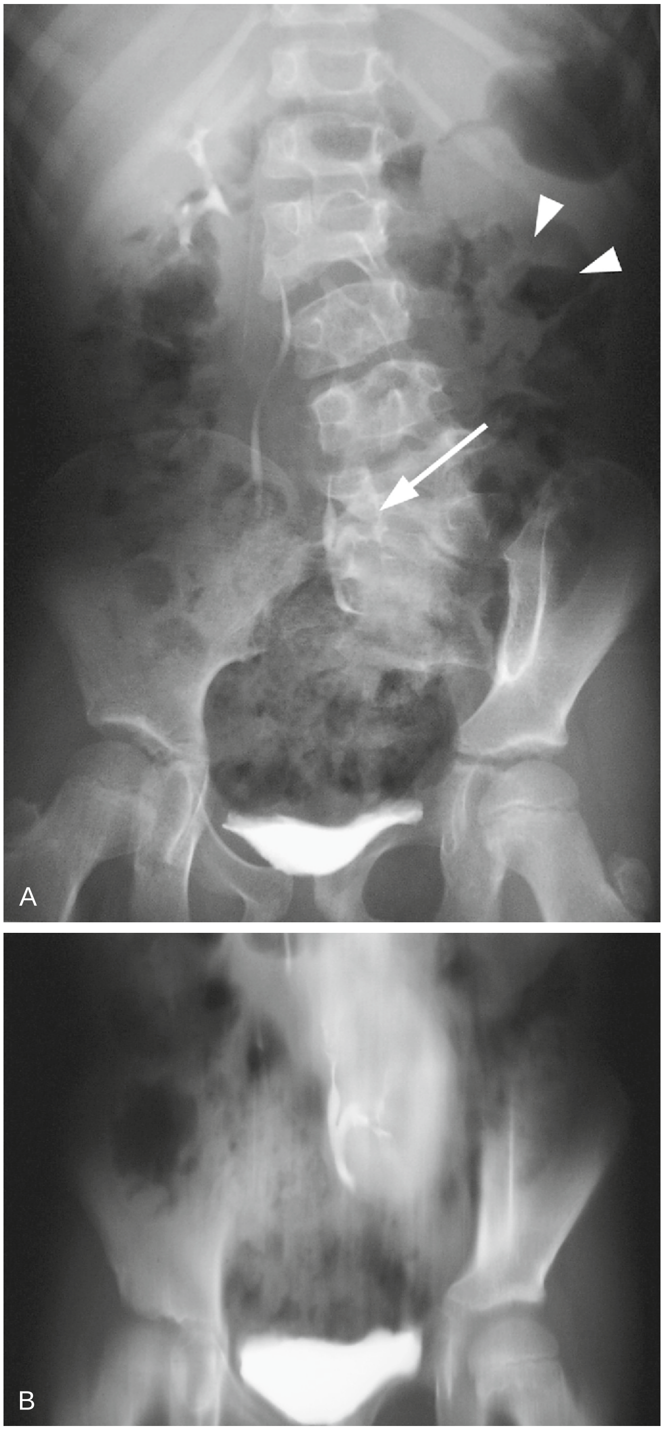

Figure 5-12 Association of renal ectopia with vertebral anomalies in a 6-year-old girl with VACTERL association and congenital scoliosis. **A,** Intravenous urogram, frontal radiograph of the abdomen shows multiple lumbosacral vertebral anomalies with congenital scoliosis. The left, nondilated collecting system of the left kidney *(arrow)* is visible in the upper pelvis. The right kidney appears normal. Note the abnormally caudal and medial position of the splenic flexure *(arrowheads)*, related to the ectopic position of the left kidney. **B,** Linear tomogram of the pelvis shows the left pelvic kidney to better advantage.

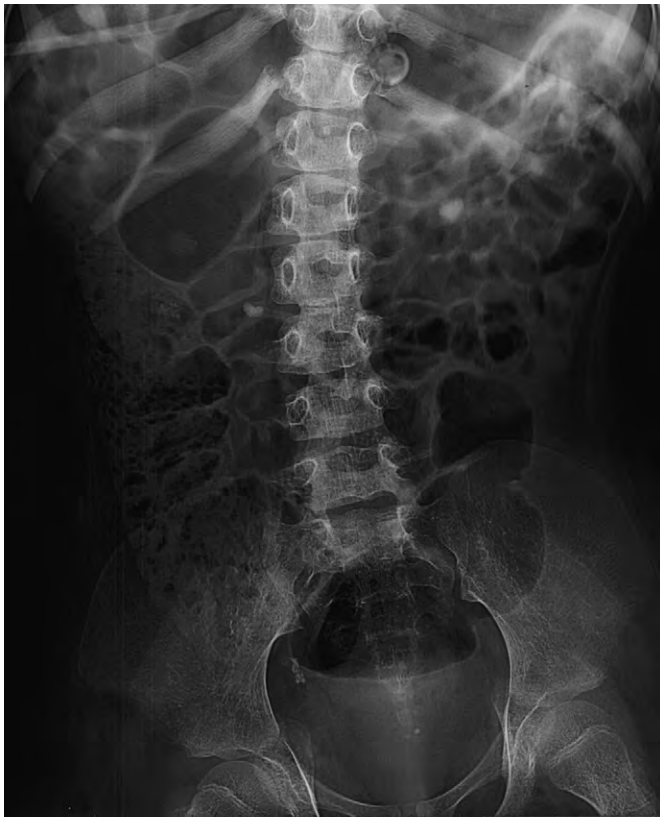

Figure 5-13 Portable abdominal radiograph of a boy in the intensive care unit, showing multiple calculi in the collecting systems of both kidneys, in the right ureter, and in the bladder.

distention of the bladder in these children can produce considerable discomfort. Instead of relaxing the bladder neck and external sphincter, younger children often attempt to void by straining, which results in depression of the bladder neck and pelvic floor, a maneuver that may paradoxically exacerbate their retention by increasing the urethrovesical angle. While the infusion of contrast material is continued, the parents should be enlisted in calming and encouraging their child. Nonverbal maneuvers that are designed to stimulate reflex micturition, such as dribbling tepid water on the perineum or running water in the sink, may be effective in some children. Plastic urinals that are designed for both sexes can be used for older children and adolescents who prefer to stand during the voiding phase of the cystogram. Older children and adolescents can be assisted in initiating micturition through the use of visual imagery techniques, and, if emptying is incomplete, intermittent fluoroscopy of the partially emptied bladder can be used to provide biofeedback and encourage further emptying.

Documenting the Examination

To minimize gonadal and total body radiation exposure, it is critical to limit total fluoroscopy time. The radiation dose can also be reduced by using contemporary digital pulse-fluoroscopy equipment and by limiting the number of overhead radiographs.[39,62,63] Substitution of radionuclide cystography (RNC), if appropriate, can also reduce radiation exposure. The main advantage of RNC is that it delivers a lower gonadal radiation dose while permitting continuous monitoring throughout filling and voiding. The sensitivities of fluoroscopic and radionuclide cystography methods for the detection of reflux are probably very similar when the procedures are performed properly. However, anatomic resolution is much superior with fluoroscopy, allowing more precise grading of reflux as well as demonstration of other pathology in the lower urinary tract.

Contrast-enhanced voiding urosonography is an alternative sonographic technique used for the detection of vesicoureteral reflux in which the patient is not exposed to ionizing radiation. In this technique, a catheter is placed in the urinary bladder, and a sonographic echo-enhancing contrast medium is infused into the bladder.[64-66] The diagnosis of reflux is based on visualization of the contrast material in the ureters or collecting systems during the later filling or voiding phases of the examination. Comparisons of this technique with conventional fluoroscopic cystography suggest a comparable sensitivity and specificity. However, the clinical role of contrast-enhanced voiding urosonography remains to be defined.

The proper location of the catheter can be quickly confirmed fluoroscopically, and the infusion of contrast material can be initiated with the patient supine.[49,63,67] Fluoroscopic images over the bladder are obtained intermittently during filling. Because ureteroceles and some vesical wall abnormalities can be obscured after the bladder is more completely filled, anteroposterior and lateral spot images of the bladder are obtained early during the filling phase. If reflux occurs, the location of the ureterovesical junction should be documented on an oblique view that includes the opacified distal refluxing ureter, bladder, and bladder neck. Additional spot images can be obtained as needed to document other abnormalities. However, routine oblique views of the bladder are unnecessary if the study is normal, except possibly later, in filling, to document that no reflux is present. During voiding, oblique spot images of the urethra are obtained in boys after the catheter has been removed, with the patient turned so that the entire urethra is visible in profile from the bladder neck to the meatus. In infants and younger children, it may also be prudent to obtain a single image of the urethra with the catheter still in place, as “insurance” against the possibility that the child might stop voiding after the catheter is removed. In girls, a spot image of the urethra and bladder neck is obtained with the patient supine. At the end of the examination, postvoid spot images of the bladder and renal beds can be obtained. Occasionally, it may also be useful to obtain a delayed postvoid radiograph of the abdomen in the child who has severe reflux and either aberrant micturition or suspected coexistent obstruction.

Postcystography Symptoms

Young children are frequently very concerned about the presence of the catheter and any discomfort that is associated with its placement or removal. Symptoms resulting from the catheterization are common in children after cystography.[52] Dysuria is most frequent, although enuresis, hematuria, urinary retention, and toileting anxiety also occur. These symptoms are usually transient, lasting in most patients for less than 24 hours. In exceptional cases, they may remain for up to 10 days or longer. Serious urethral or vesical trauma is quite rare during catheterization for cystography, although urethral stricture and perforation of the urethra or bladder can occur.

Normal and Abnormal Appearances of the Bladder

The bladder base rests on the pelvic floor, which in infants and children is normally at the level of the superior margin of the symphysis pubis (Fig. 5-14). As the bladder fills, the anterior compartment expands anteriorly and upward into the abdomen.[39,68,69] A small portion of the anterior compartment also projects inferiorly, just anterior to the bladder neck, and is best appreciated on VCUG in the lateral projection. Occasionally, two anterolateral recesses can also be identified, which are often referred to as “bladder ears.” When the bladder neck opens during voiding, the posterior compartment becomes funnel-shaped, and the anterior compartment collapses uniformly in all directions. The bladder wall normally has a smooth contour on cystography when distended, although it can be slightly irregular, particularly posteroinferiorly, when not distended.

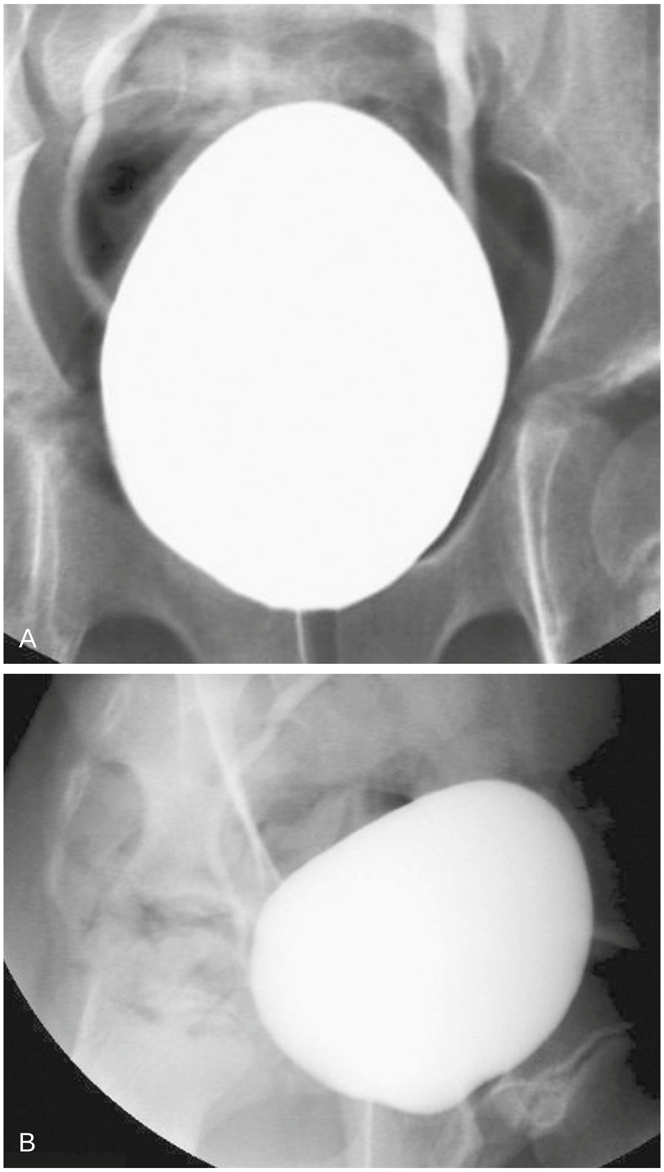

Figure 5-14 Normal appearance of the urinary bladder on voiding cystourethrogram in a 5-year-old girl with bilateral low-grade vesicoureteral reflux. Frontal **(A)** and lateral **(B)** views of the filled urinary bladder. The bladder shape and position are normal, and the bladder wall is smooth.

In neurogenic dysfunction, the bladder often appears elongated vertically and can be thickened and trabeculated with numerous diverticula (Fig. 5-15).[39,69,70] Discoordination between the bladder-trigone and bladder neck–external

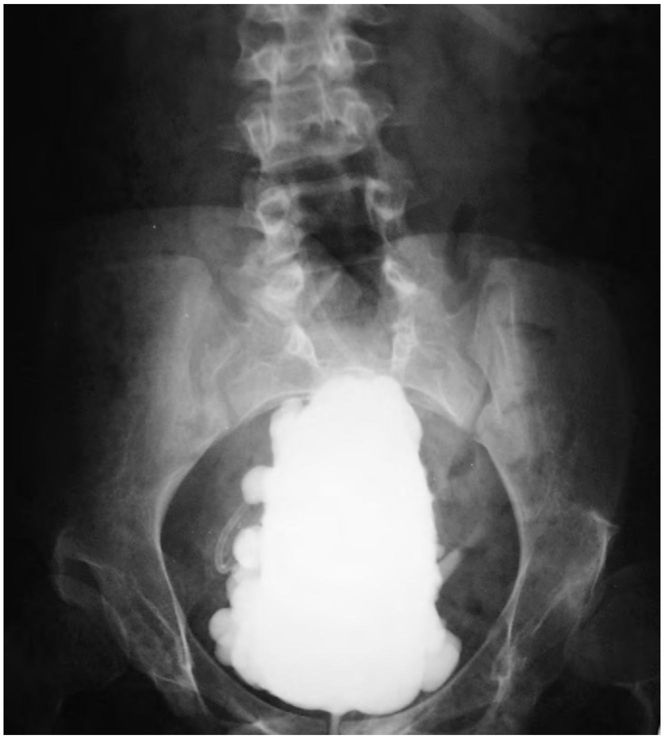

Figure 5-15 Neurogenic bladder. Voiding cystourethrogram in a 12-year-old girl with myelomeningocele. Frontal image of the abdomen and pelvis with the bladder distended shows that the bladder has a vertically elongated configuration with a markedly irregular and thickened wall and numerous diverticula. The sacrum is markedly dysraphic, and the distal end of a ventriculoperitoneal shunt is visible in the pelvis on the right side.

sphincter is common. Children with flaccid paralysis often have thinner, smoother bladder walls. Paralysis of the pelvic floor can lead to prolapse of the bladder base below the upper margin of the symphysis, as well as rectal and vaginal prolapse.[69] Conversely, elevation of the bladder base above the symphysis pubis is a common finding after bladder neck surgery, bladder augmentation, or continent vesicostomy.

Extrinsic impressions on the bladder are best visualized on frontal and lateral views of the pelvis that are obtained during the early filling phase by VCUG. On the lateral projection, the pelvis can be divided anatomically in relation to the urinary bladder into three compartments: (1) the rectal/retrorectal compartment, which includes the sacrum, the retrorectal/presacral space, and the rectum itself; (2) the prerectal space between the bladder and the rectum; and (3) the prevesical/retropubic space between the bladder and the symphysis pubis. Marked rectal distention in children who have imperforate anus or Hirschsprung's disease, and occasionally even in children with severe functional constipation, can produce deep indentation of the posterior wall of the bladder and bladder neck or even displace the entire bladder forward. Retrorectal masses, such as sacrococcygeal teratoma, anterior meningocele, and other malignant primary sacral tumors, can compress the rectum and also indent or displace the bladder anteriorly. Masses in the prerectal (retrovesical) space include refluxing or obstructed megaloureter, ureterocele, hydrocolpos and uterovaginal masses, ovarian cysts or masses, and loculated fluid collections in the cul-de-sac, such as appendiceal abscess. Urachal remnants are the most common abnormalities to indent the anterior wall of the bladder. Prevesical urinomas and hematomas are occasionally seen with spontaneous or traumatic bladder perforation.

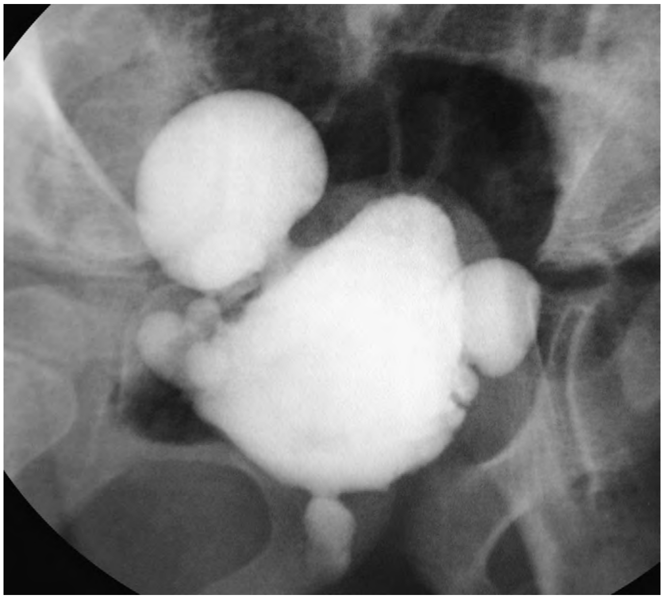

Figure 5-16 Multiple bladder diverticula. Voiding cystourethrogram in a 7-year-old boy with Williams' syndrome.

Most congenital bladder diverticula represent saccular outpouching at focal areas of bladder wall weakness; they are most often paraureteral in location.[71,72] The size of the diverticulum at any given time is related to the degree of eversion of the bladder wall and can vary dramatically through the filling-voiding cycle and between examinations.[73] The relationship between paraureteral diverticula and secondary vesicoureteral reflux is very dynamic, and the reflux can be intermittent. Aberrant micturition is another important complication of multiple or large bladder diverticula; it can be exacerbated by the presence of reflux. Rarely, a very large diverticulum that projects posteroinferiorly behind the bladder neck can cause bladder outlet obstruction.[74] Congenital diverticula at the bladder dome anteriorly are usually urachal in origin. Acquired bladder diverticula can occur anywhere along the bladder wall and are common in children who have neurogenic bladder dysfunction or "non-neurogenic" dysfunctional voiding disorders, as well as in children who have long-standing bladder outlet or urethral obstruction. Acquired diverticula also occur commonly in boys with prune-belly syndrome and in a diverse group of disorders that are associated with chronic megalocystis, such as nephrogenic diabetes insipidus and the megalocystis-microcolon-intestinal hypoperistalsis syndrome. Bladder diverticula also occur in children and adults with a number of connective tissue disorders that affect the bladder wall, such as Williams' syndrome (Fig. 5-16), Ehler-Danlos syndrome type IX, and Menkes kinky-hair syndrome. Eversion of the bladder wall at areas of postoperative weakness can also produce the appearance of a bladder diverticulum.

Variations in the degree of distention of a ureterocele occasionally lead to confusion with bladder diverticulum.[75,76] Most ureteroceles are maximally distended and, therefore, are most easily detected by VCUG early during bladder filling (Fig. 5-17). Later in the filling phase and during voiding, when the intravesical pressure is higher, many ureteroceles become smaller or even seem to disappear as they are compressed

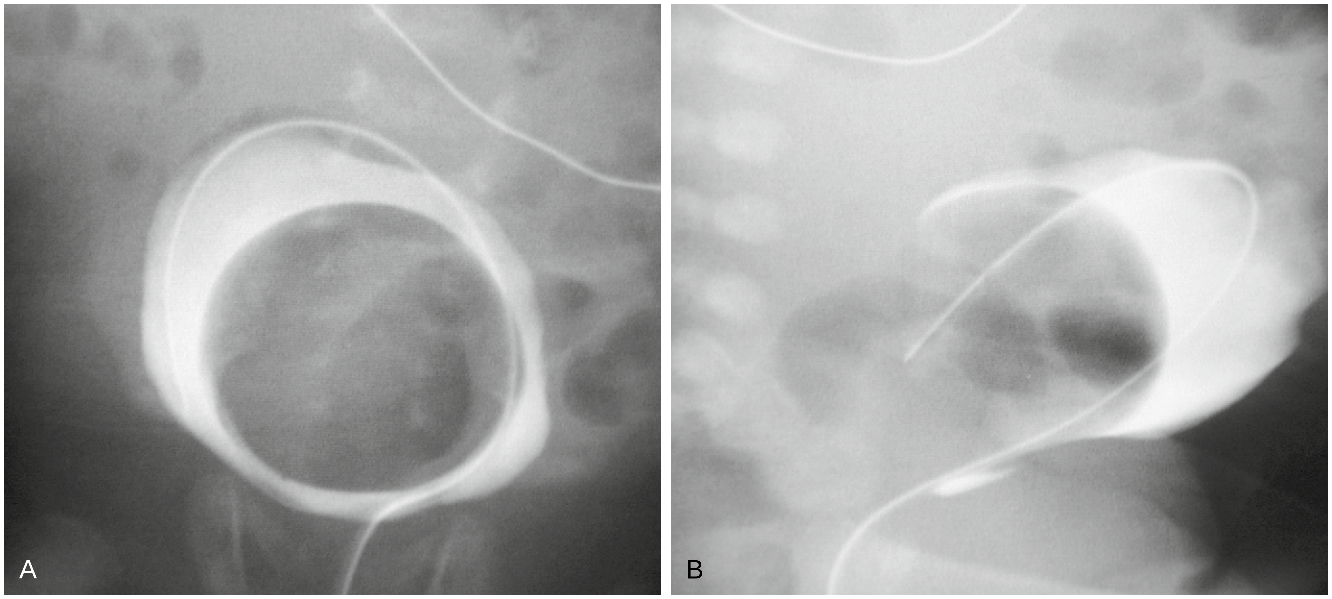

Figure 5-17 Very large single-system ureterocele. Voiding cystourethrogram in a newborn boy with severe right hydroureteronephrosis. Frontal **(A)** and lateral **(B)** views of the partially filled urinary bladder show a very large, smoothly rounded filling defect posteriorly along the floor of the bladder, typical of a large ureterocele.

against the bladder wall ("ureterocele effacement"). If the wall of the ureterocele intussuscepts upward into its ureter ("ureterocele eversion"), the appearance can mimic that of a paraureteral diverticulum (Fig. 5-18). A prolapsing ureterocele appears on cystography as a lobular mass distending the bladder neck and urethra; it can even protrude from the urethral meatus in a girl and appear as an interlabial mass.[77]

When reflux is present (Figs. 5-19 and 5-20), the appearance and axis of the collecting system should be carefully evaluated to detect duplication anomalies of the collecting system and ureter and to identify calyceal distortion secondary to renal scarring. The most widely used system for grading the severity of reflux is that described by the International Reflux Study in Children (IRSC)[78]:

I Reflux to the ureter only
II Reflux to the collecting system without dilatation of the ureter or collecting system
III Reflux to the collecting system with mild dilatation of the ureter or collecting system or both, but with preservation of the concave appearance of the calyces
IV Reflux to the collecting system with moderate dilatation of the ureter and collecting system and blunting of the calyces
V Gross dilatation of ureter and collecting system with obscuration of calyceal shape and loss of the papillary impressions

Grading of reflux on RNC (Fig. 5-21) uses a 3-point scale; it is less precise and somewhat more subjective but does correspond roughly to the IRSC system:

I Reflux to ureter only (corresponds to IRSC grade I)
II "Mild" reflux to the ureter and collecting system (corresponds to IRSC grades II-III)
III "Marked" reflux to the ureter and collecting system (corresponds to IRSC grades IV-V)

Intrarenal reflux (pyelotubular backflow) due to papillary incompetence is another very important cystographic observation.[67,78] However, because renal parenchymal opacification caused by intrarenal reflux is often subtle, it is probably significantly under-reported. Even when it is not visible on imaging studies, intrarenal reflux of infected urine is presumed to be the mechanism by which bacteria in the collecting systems gain access to the renal parenchyma in ascending pyelonephritis.[79] The polar predilection of acute ascending pyelonephritis is partially explained by the fact that papillary incompetence is more common in compound pyramids, which are more frequent in the upper and lower renal poles.

Normal and Abnormal Appearances of the Urethra

Distention of the proximal female urethra at peak flow during voiding ("spinning top" urethra) is a normal finding (Fig. 5-22) that by itself does not suggest underlying bladder dysfunction. Whether this appearance occurs more often in girls who have some degree of bladder-sphincter dyssynergia remains controversial.[80,81] Vaginal reflux is also common (Fig. 5-23), particularly in neonates and younger infants, in whom it is considered to be a normal finding.[82] In toilet-trained girls, vaginal reflux can limit the usefulness of clean-catch urine specimens due to contamination by vaginal flora, and it can also be an important cause of postmicturition incontinence. In a girl who presents with persistent incontinence, performance of multiple cycles of filling and voiding during a cystogram may increase the visibility of small amounts of reflux into an ectopic ureter that inserts into the urethra.[61]

VCUG is the imaging "gold standard" for evaluating the anatomy of the male urethra (Fig. 5-24). The prostatic urethra is embedded in the body of the prostate gland and extends from the bladder neck proximally to the external sphincter distally. The verumontanum forms the ventral wall of the prostatic urethra and contains the openings of the prostatic utricle and ejaculatory ducts. Narrowing of the midprostatic urethra at the intermuscular incisura is an occasional, normal observation on VCUG and should not be mistaken for posterior urethral valves. Similarly, the plicae collicularis represent normally thin, nonobstructing folds along the distal margin

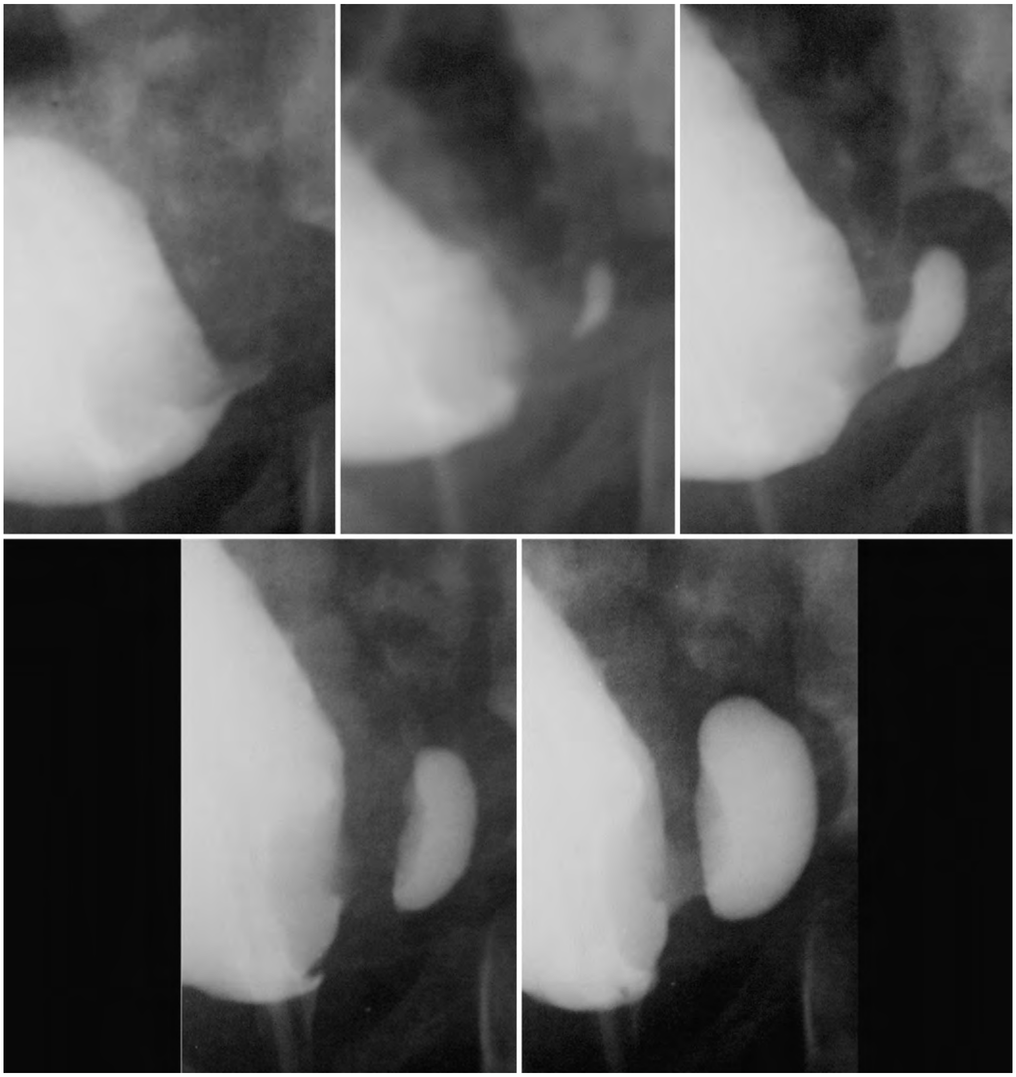

Figure 5-18 Everting left upper-pole ureterocele mimicking a left paraureteral diverticulum on voiding cystourethrography in a newborn boy with antenatally detected left duplex kidney and upper-pole hydronephrosis. The series of five right posterior oblique images of the left side of the bladder during bladder filling shows a left ureterocele that initially appears as a filling defect *(top row)*. As the bladder is distended, the ureterocele is initially effaced and then everts, projecting outside of the bladder and mimicking a paraureteral diverticulum *(bottom row)*.

of the verumontanum, near the junction of the prostatic and membranous portions of the urethra. The penile and bulbous segments of the anterior urethra are separated by the suspensory ligament (Fig. 5-25).

Posterior urethral valves are the most common cause of urethral obstruction in the male infant and child (Fig. 5-26).[39,83] The degree of obstruction is variable but is frequently severe, with the urinary stream emerging from between the valves along the ventral surface of the base of the verumontanum. During attempts at voiding, the posterior urethra dilates and the valves balloon outwardly. Reflux into prostatic or ejaculatory ducts, or both, is also common. The bladder neck is usually hypertrophied and the bladder wall thickened and trabeculated, with numerous bladder diverticula. The diagnosis of posterior urethral valves by cystography requires visualization of the urethra in a steep oblique projection during attempted micturition after the catheter has been removed. However, if bladder wall contractility is severely impaired, the child may be unable to generate sufficient forward force during voiding to distend the posterior urethra and visualize the valves. Aberrant micturition secondary to associated vesicoureteral reflux and severe hydroureteronephrosis can further impair distention of the urethra. When reflux is present, it is frequently associated with severe renal dysplasia and reduced renal function. In such cases, intraparenchymal reflux leads to opacification of dilated and ectatic collecting tubules that can persist for hours or even days.[84]

In anterior urethral valves, a congenital ventral membrane partially obstructs the urethra distal to the external sphincter (Fig. 5-27).[39,85] With voiding, the membrane balloons outward toward the meatus, beneath the ventral aspect of the urethra, causing a “wind-sock” type of urethral obstruction. The urethra proximal to the “valves” is dilated, and there are secondary postobstructive changes in the bladder and upper urinary tract, similar to those encountered in posterior urethral valves.

Urethral strictures in children occur almost exclusively in boys and are mostly post-traumatic in origin. Straddle injuries produce strictures of the bulbar urethra. Strictures of the membranous and prostatic urethra result from urethral disruption associated with injuries to the inferior pelvis and pelvic floor. Postinfectious urethral strictures are very rare

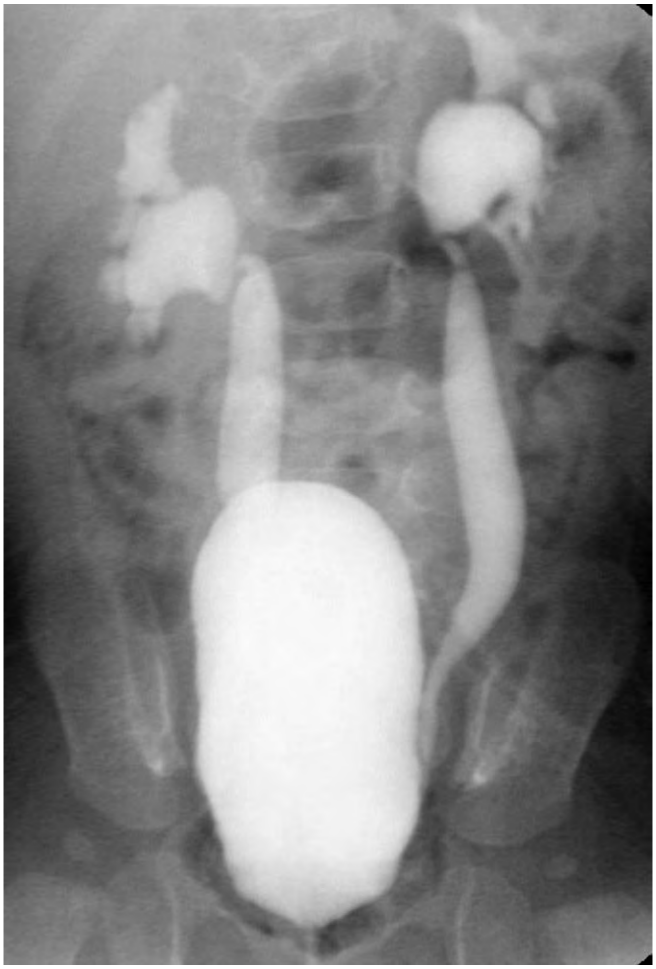

Figure 5-19 Bilateral grade III vesicoureteral reflux. Voiding cystourethrogram in a 10-month-old girl with multiple urinary tract infections. The renal pelves and calyces are distended but not distorted, and the renal axes are normal.

in children, as are neoplastic strictures. Congenital strictures of the penile urethra occur rarely. Although the narrowing at the site of a stricture is usually readily visualized on an antegrade VCUG, the length of the stricture can be accurately determined only by comparison of antegrade and retrograde urethral contrast studies. Occasionally, the appearance of a stricture of the proximal penile urethra can be simulated by upward pressure of the urinal against the ventral aspect of the base of the penis (“urinal artifact”).[68] Moving the lip of the urinal away from the penis relieves the obstruction in such cases.

When the orifice of a Cowper duct is incompetent, the duct will fill during VCUG, appearing as a tubular structure of variable diameter extending proximally toward the urogenital diaphragm, beneath the ventral surface of the penile urethra (Fig. 5-28).[86] Opacification of the gland itself can also occur. Conversely, obstruction of the Cowper duct orifice can result in a retention cyst, which appears as a smoothly rounded filling defect on the floor of the bulbar urethra. Although these abnormalities are often encountered as incidental findings, Cowper duct reflux can be associated with postmicturition incontinence when the duct drains, and both anomalies have been implicated as potential causes of dysuria and microhematuria in some boys.

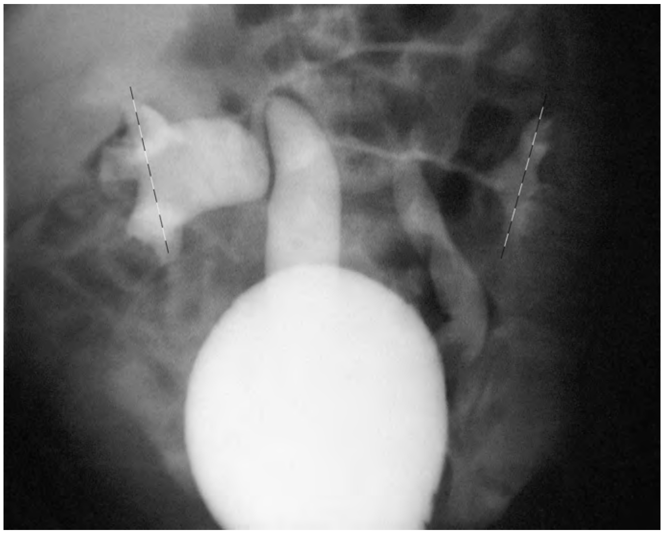

Figure 5-20 Bilateral complete duplex kidneys with bilateral lower-pole vesicoureteral reflux. Voiding cystourethrogram in a 1-month-old girl with mild right antenatal hydronephrosis. Note that the most superior visible calyx in each kidney is very far from the ipsilateral pedicle and the renal axes *(hatched lines)* are reversed bilaterally, suggesting that only the lower pole is opacified on each side.

CROSS-SECTIONAL IMAGING: COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

The past several decades have seen rapid growth in the application of both CT and magnetic resonance imaging (MRI) in the evaluation of a widening spectrum of pediatric genitourinary disorders. CT has the advantages of speed, simplicity, and widespread availability. However, CT is also the primary source of medical radiation exposure in children and the largest source other than background.[87] Although CT accounts for less than 5% of all imaging studies, more than 60% of all medical radiation exposure results from CT. Evidence for an increased risk of cancer and other disease secondary to exposure to low-dose radiation is derived from long-term follow-up of atomic bomb survivors and from data on medical and occupational exposures. The estimated lifetime risk of radiation-induced fatal cancer is 1:1000 from a single pediatric CT examination, and the risk is cumulative when multiple examinations are performed. Less is known about the potential health and economic consequences of nonfatal cancer and other disorders resulting from low-level radiation. Evidence for greater vulnerability of organs and tissues in growing children to radiation-induced cancer should raise particular concern in pediatrics. Because most radiation-induced cancers do not manifest until decades after exposure, and because children generally have a longer residual life expectancy than adults, they also have a longer period of time in which to manifest radiation-related disease. The first step in limiting medical radiation exposure is to consider whether CT is the most appropriate modality. When provided with adequate clinical information, the pediatric radiologist might in some cases suggest an alternative modality that does not involve ionizing radiation, such as US or MRI. However, even when CT is appropriate, access to clinical information can help the pediatric radiologist customize the study so as to best address the important clinical issues while at the same time minimizing the radiation dose to the patient.

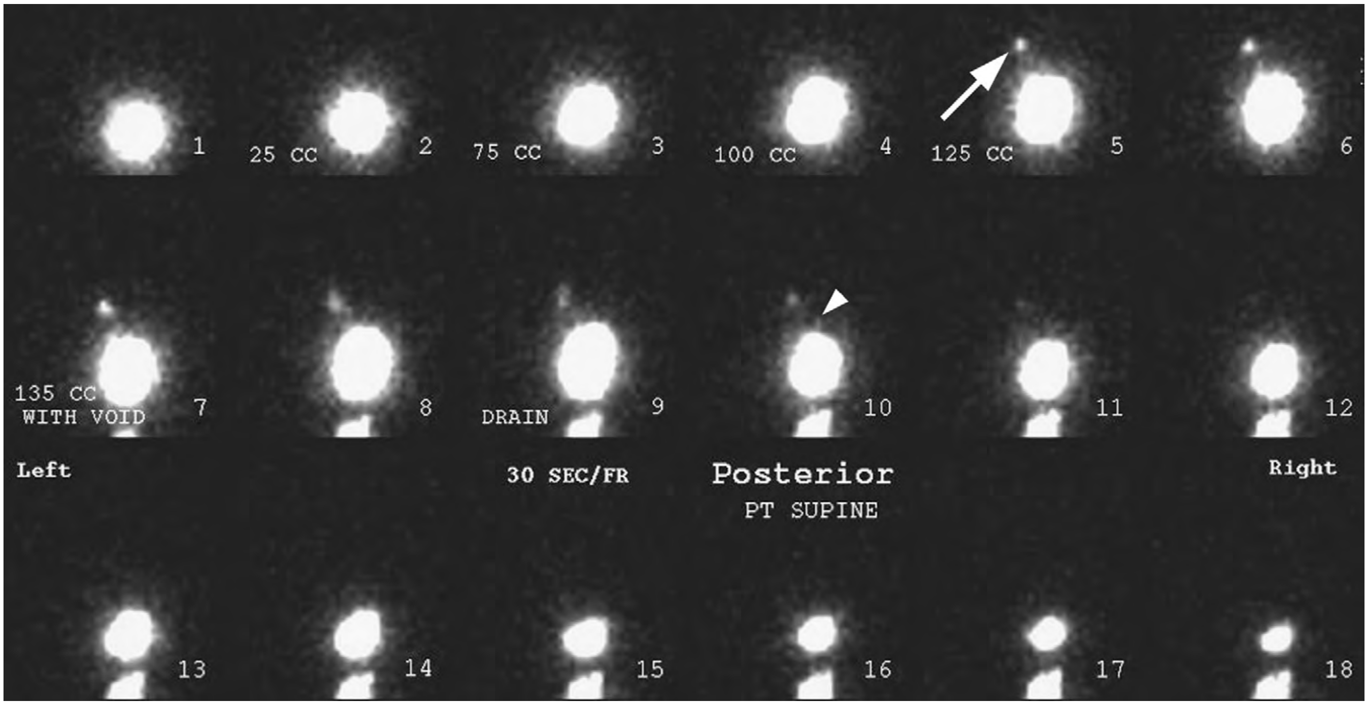
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Figure 5-21 Bilateral vesicoureteral reflux. Radionuclide cystogram in a 2-year-old girl with multiple previous urinary tract infections. The series of 18 30-second posterior images obtained during bladder filling and emptying show persistent reflux to the left collecting system *(arrow)* and subtle, transient reflux into the distal right ureter that is visible only on a single image *(arrowhead)*.

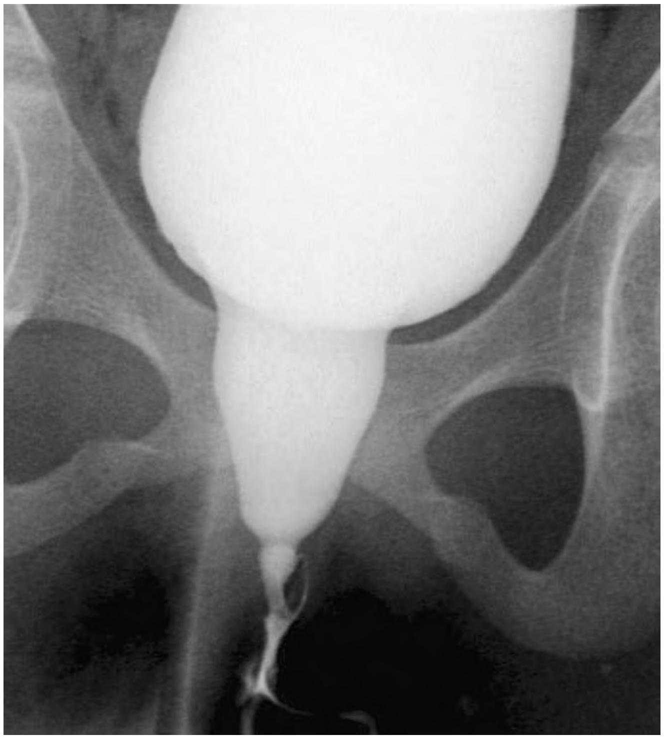

Figure 5-22 “Spinning top” appearance of the female urethra. Voiding cystourethrogram (VCUG) in a 10-year-old girl with recurrent urinary tract infections. Dramatic distention of the female urethra at peak flow during voiding is a common, normal finding on VCUG and does not necessarily indicate dyssynergy.

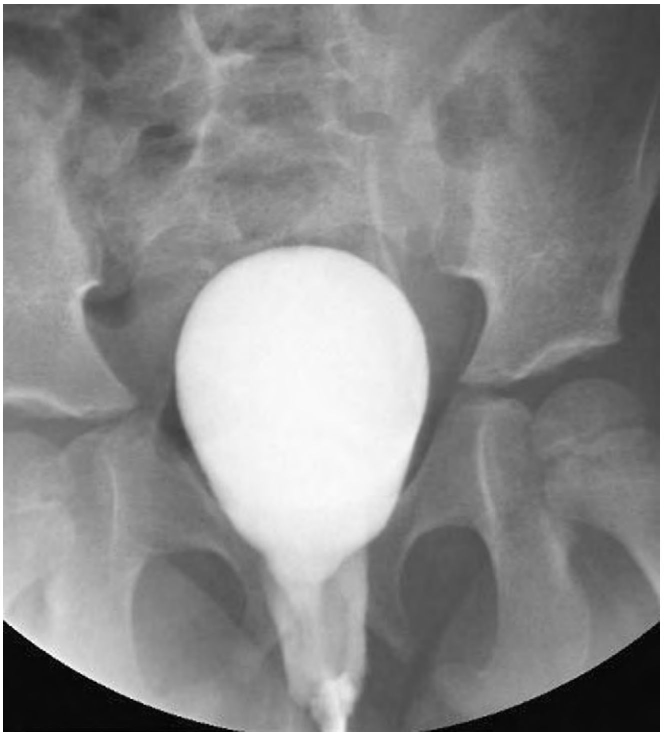

Figure 5-23 Vaginal reflux. Voiding cystourethrogram in a 4-year-old girl. Although vaginal filling during cystography has been attributed to voiding in the supine position, it can also occur in some girls when they are seated or even standing upright, and it can be a cause of postmicturition incontinence.

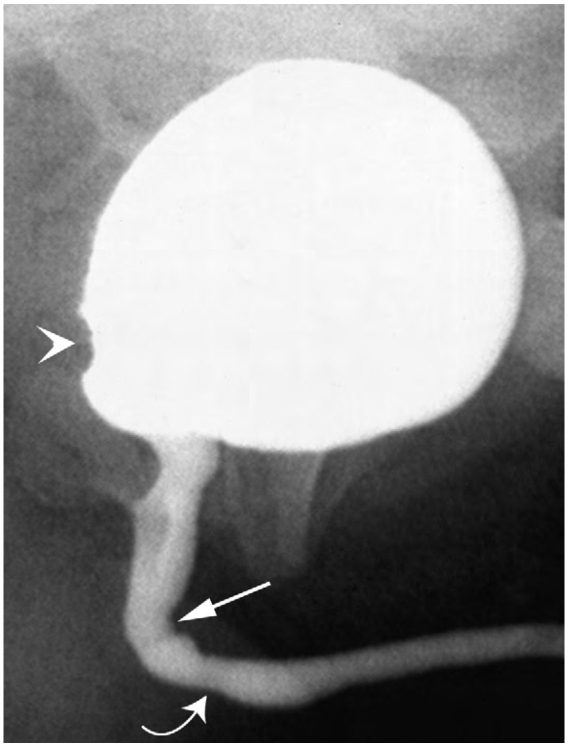

Figure 5-24 Voiding cystourethrogram shows a normal voiding phase in a boy. Normal notching of the interureteral ridge of the bladder *(arrowhead)* and of the indentation at the level of the pelvic floor *(straight arrow)* is seen. The notching of the external sphincter is below *(curved arrow)*.

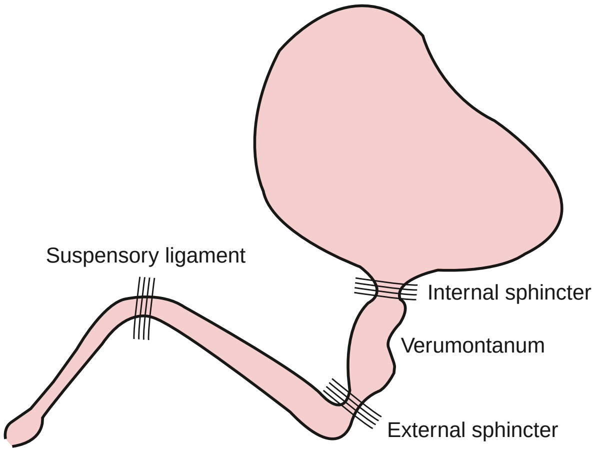

Figure 5-25 Drawing of the normal and permanent narrowings in a normal male urethra.

Exquisite soft tissue contrast and direct multiplanar capabilities are important advantages of MRI. Moreover, MRI does not require intravenous administration of iodinated contrast material, nor is the patient exposed to ionizing radiation. The excellent safety profile of gadolinium-based MRI contrast agents, compared with the iodinated media used for conventional urography and CT, are other significant advantages of MRI. Although the administration of gadolinium-based contrast agents is contraindicated in patients with renal insufficiency because of the risk of nephrogenic systemic fibrosis, non-enhanced MRI can still be performed in these patients.[88] MRU provides higher temporal, spatial, and contrast resolution than traditional IVU, and it combines anatomic and functional evaluations of the urinary tract into a single test that does not use ionizing radiation.

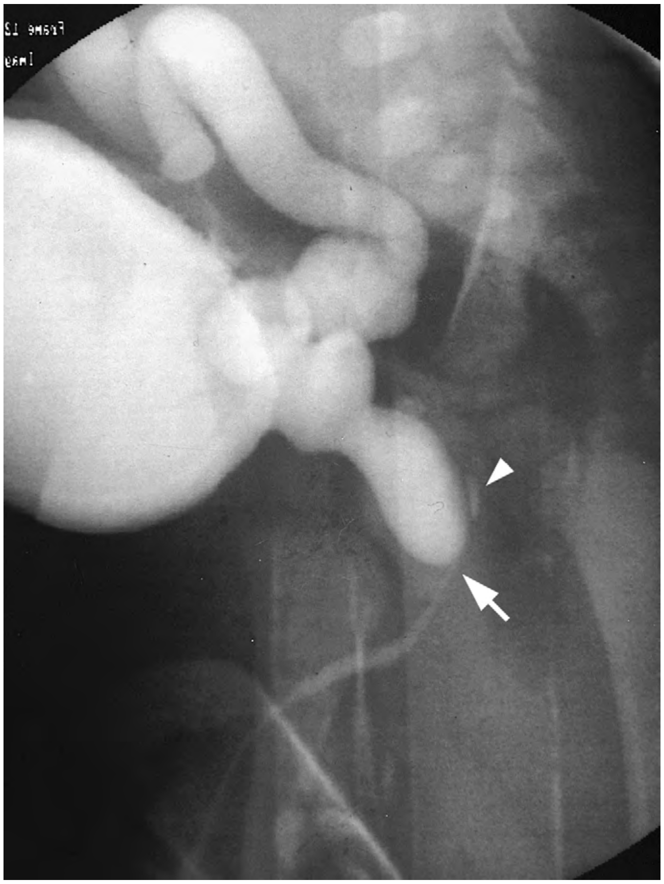

Figure 5-26 Posterior urethral valves. Voiding cystourethrogram in a newborn boy with severe bilateral antenatal hydronephrosis and renal dysplasia. Steep right posterior oblique view of the bladder and urethra during voiding shows the marked transition in caliber of the urethra at the level of the posterior urethral valves *(arrow)*, just distal to the verumontanum. The bladder neck is hypertrophied, and the posterior bladder wall is irregular. The posterior trigone is markedly distorted, and there is reflux into a dilated and tortuous ureter. The prostatic utricle is also opacified *(arrowhead)*.

The need for procedural sedation, and occasionally general anesthesia, to eliminate motion-related degradation in image quality and associated motion-related artifacts remains an important limitation of MRI, particularly in infants and younger children and in the developmentally challenged. Although procedural sedation and anesthesia services are routinely provided in pediatric centers and are highly efficacious and safe, the availability of such services outside the dedicated pediatric medical imaging environment is more limited. Continuing improvements in MRI technology and faster imaging protocols that reduce acquisition times should diminish the necessity, or at least the duration, of sedation in some children in the future.

TECHNIQUE AND NORMAL APPEARANCES

Computed Tomography

On non-enhanced CT examinations, renal parenchymal attenuation is normally very homogeneous (32 to 60 Hounsfield units [HU]), with no differentiation between the renal

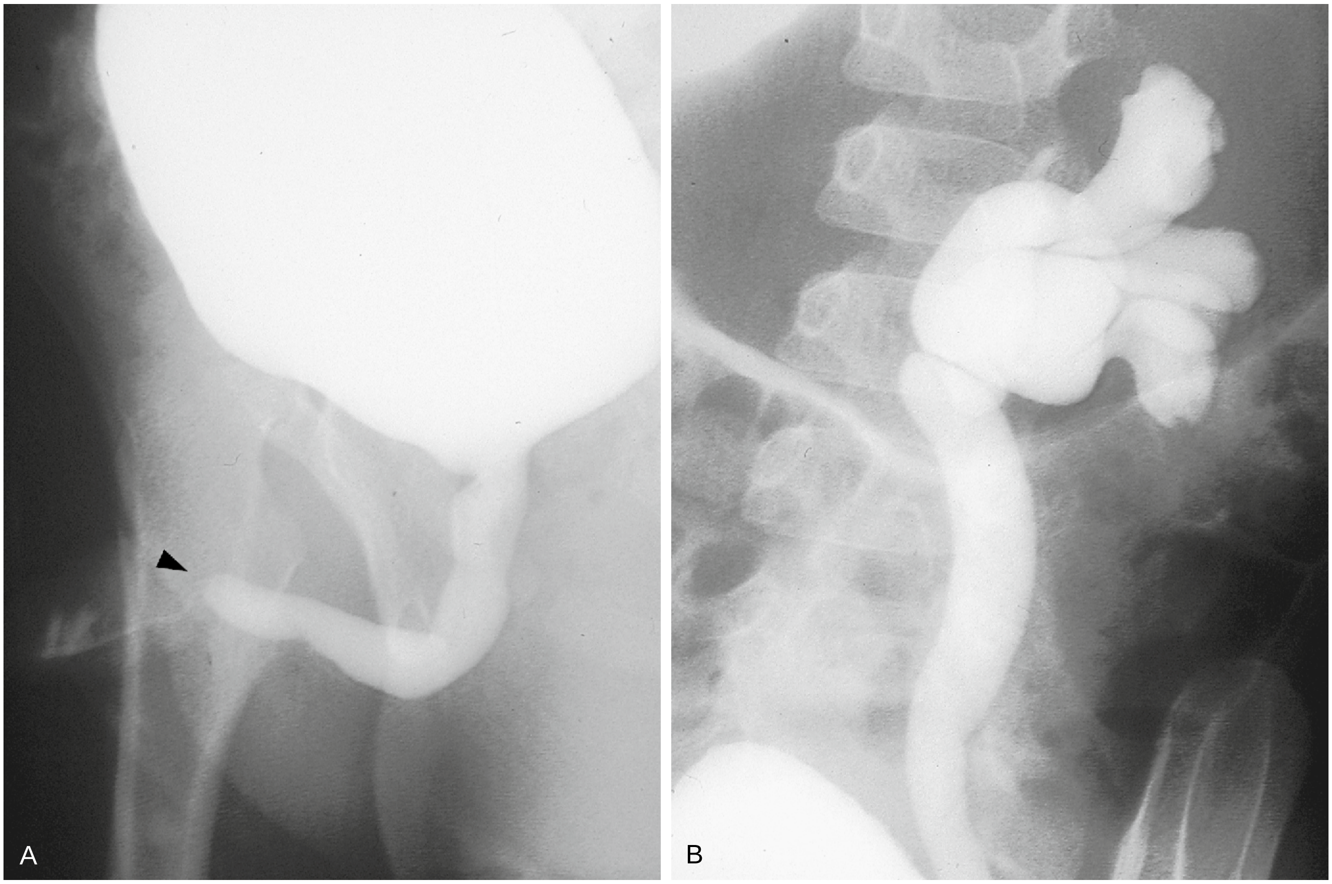

Figure 5-27 Anterior urethral valves with high-pressure left vesicoureteral reflux in a 4-year-old boy. **A,** Steep right posterior oblique view of the bladder and urethra during voiding shows that the posterior and proximal anterior urethra are dilated, with an abrupt transition in caliber at the middle anterior urethra *(arrowhead)*. At the site of the obstruction, the urethra is ballooned distally, with a wind-sock appearance, characteristic of anterior urethral valves. **B,** Image obtained during voiding shows dilating, high-pressure left vesicoureteral reflux with calyceal blunting and distortion.

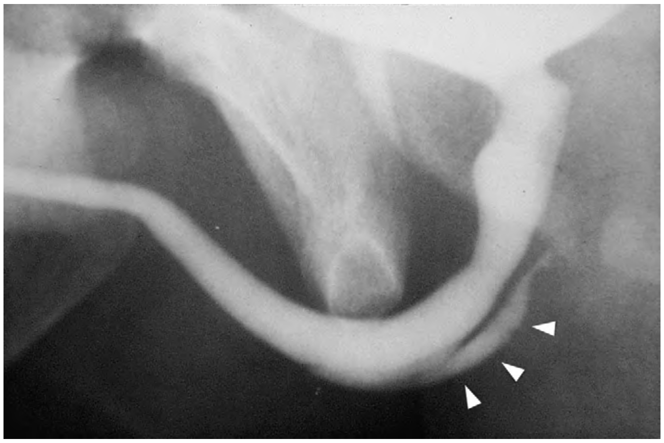

Figure 5-28 Cowper duct reflux. Voiding cystourethrogram in a 9-year-old boy with dysuria and microhematuria. Steep right posterior oblique view of the urethra during voiding shows opacification of a narrow tubular structure extending proximally from the ventral surface of the middle anterior urethra toward the urogenital diaphragm *(arrowheads)*.

medulla and cortex (Fig. 5-29).[89-91] The renal hilum and pelvis are readily identified, but nondilated calyces and infundibula usually are not visible on precontrast images, except occasionally as faint, irregular areas of fluid attenuation within the parenchyma. In older children and adults, the main renal vessels are easily seen, even on non-enhanced studies, but they may not be identifiable separate from the renal pelvis in infants and younger children unless contrast material is used.

Renal parenchymal attenuation on postcontrast CT images depends on the dose and rate of contrast administration, the timing of the images in relation to the contrast bolus, and the state of renal function (Fig. 5-30). After rapid intravenous administration of contrast material as a single bolus, the aorta and renal arteries are opacified first, followed by the renal veins and inferior vena cava. The renal cortex then enhances, appearing as a regular, 4- to 6-mm thick, peripheral band of higher attenuation, with columns of Bertin extending centrally between the renal lobes. Corticomedullary differentiation is maximal during this phase, with the medullary pyramids appearing as polygonal structures of relatively lower attenuation, regularly distributed within the enhancing cortex. As medullary enhancement progresses, corticomedullary differentiation declines until the renal parenchyma becomes diffusely and homogeneously dense. The attenuation of the parenchyma gradually declines after contrast material appears in the collecting system. Appropriate timing of the imaging in relation to contrast bolus and phase of parenchymal enhancement is critical, because the relative attenuation and conspicuity of renal parenchymal lesions varies as renal cortical and medullary attenuation changes.

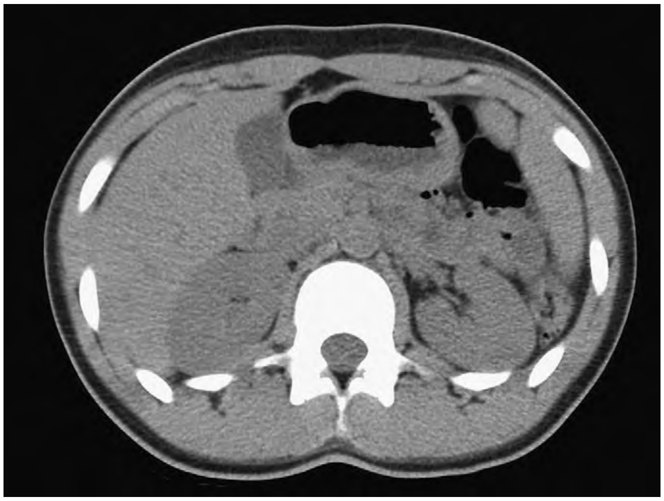

Figure 5-29 Normal noncontrast axial computed tomographic scan through the kidneys at the level of the left renal vein in a young child. The renal hilum and pelvis are readily identified. However, the renal parenchyma is very homogeneous in attenuation, with no differentiation between the renal medulla and cortex.

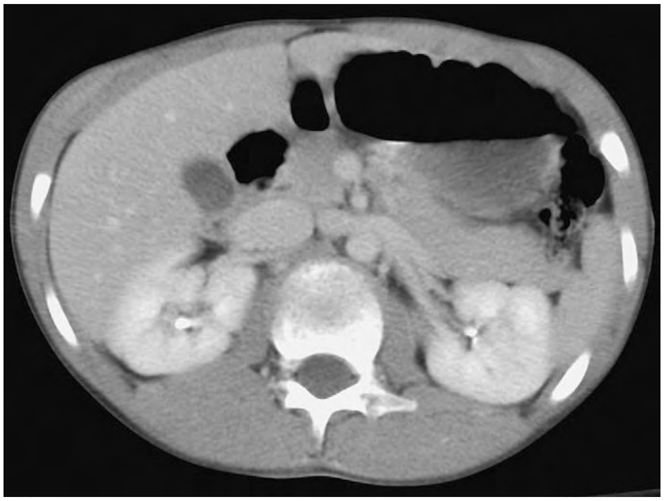

Figure 5-30 Normal postcontrast axial computed tomographic scan through the kidneys at the level of the left renal vein in a young child during the early excretory phase. The renal cortex is still enhanced, although less so than the medullary pyramids, and a small amount of contrast material is beginning to appear in the collecting systems. Note that the aorta and its branches and the inferior vena cava and left renal vein are also still somewhat opacified.

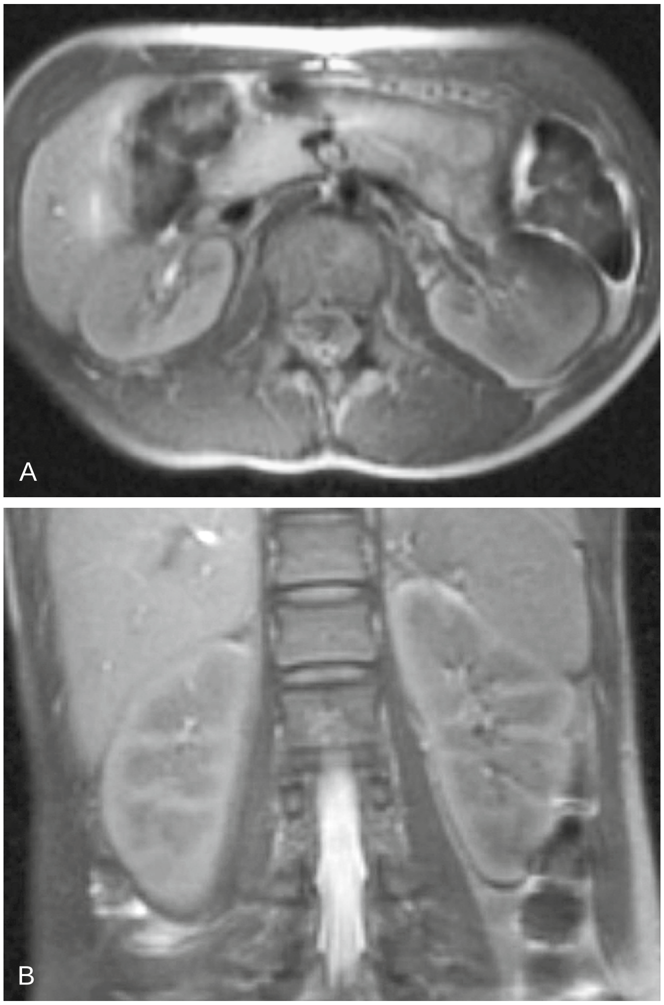

Figure 5-31 Normal T1-weighted (fat-suppressed) non–contrast-enhanced axial **(A)** and coronal **(B)** magnetic resonance images of the kidneys in a young child show some corticomedullary differentiation, with the cortex having slightly greater signal intensity than the medullary pyramids.

Magnetic Resonance Imaging

On MRI, corticomedullary differentiation is well demonstrated on spin-echo T1-weighted images, with the cortex having higher signal intensity than the medullary pyramids (Fig. 5-31).[91,92] The difference in signal intensity between cortex and medulla is most pronounced in neonates and young children and decreases with age. Corticomedullary differentiation is also typically well defined on inversion recovery sequences, but it can vary depending on the state of hydration. However, on very heavily T1-weighted images, the corticomedullary differentiation becomes less well defined as the signal intensities of both the cortex and medulla decline. The high signal intensity that is visible in the renal hilum in adults is not as prominent in infants and young children, who have less hilar fat. The renal collecting system and ureter have low signal intensity on spin-echo sequences because of the long T1 relaxation time of urine. The renal artery and vein also usually have very low signal intensity, related to rapid flow of blood into and out of the kidney, although an intraluminal signal normally can be identified when flow within the renal vessel is slower. This artifact can also occur secondary to flow-related enhancement when images are obtained of the vessel in cross section.

On T2-weighted sequences, the renal cortex and medulla both have increased signal intensity (Fig. 5-32).[91,92] However, corticomedullary differentiation is less well visualized, because the cortex is only slightly higher in signal intensity than the medulla. The perirenal fat also appears bright on T2-weighted sequences and Gerota's fascia appears as a low-intensity line separating the perirenal and pararenal spaces. A low-signal-intensity line is occasionally visible along one side of the kidney, with a symmetric high-signal-intensity line along the opposite side.[93] This represents a chemical shift misregistration artifact occurring at the interface between the kidney and the adjacent perirenal fat and should not be attributed to a rim of calcification.

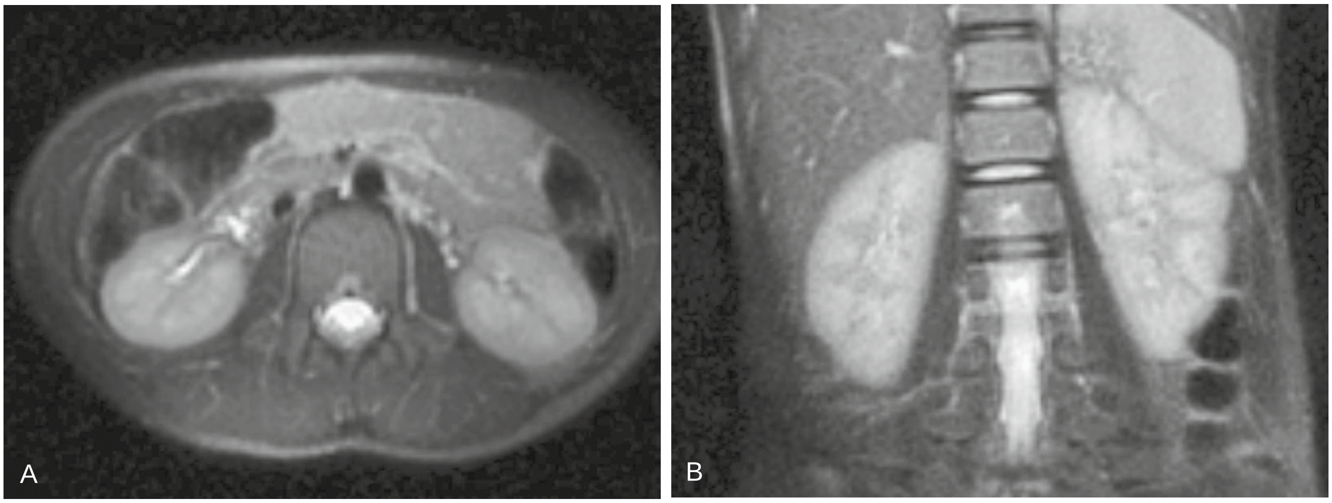

Figure 5-32 Normal T2-weighted (fat-suppressed) non–contrast-enhanced axial **(A)** and coronal **(B)** magnetic resonance images of the kidneys in a young child show somewhat greater signal intensity of the renal parenchyma than on the T1-weighted images, but with little, if any, corticomedullary differentiation.

Contrast-Enhanced Renal Magnetic Resonance Imaging and Magnetic Resonance Urography

Gadolinium chelates, such as gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA), are ideal for studying renal morphology and function, because they are filtered by the glomerulus and excreted by the renal tubules (Fig. 5-33).[94,95] The physiologic behavior of gadolinium chelates is primarily governed by the biochemical properties of the DTPA ligand, which are very similar to those of inulin. DTPA is freely filtered by the glomerulus and is neither reabsorbed nor secreted by the renal tubules. Because the paramagnetic properties of gadolinium cause marked T1 and T2 shortening, renal uptake and excretion of Gd-DTPA can be readily monitored with T1-weighted images. Cortical enhancement primarily reflects renal perfusion and glomerular filtration, whereas medullary enhancement and opacification of the collecting system depend on glomerular filtration as well as renal tubular secretion and absorption. Because the superior spatial resolution of MRI permits clearer discrimination of cortical from medullary enhancement, MRI provides more precise assessments of both renal perfusion and glomerular filtration and has the potential to noninvasively differentiate between glomerular and tubulointerstitial pathology.[95,96] Unfortunately, gadolinium-based MRI contrast agents cannot be safely used in patients with renal insufficiency because of the risk of nephrogenic systemic fibrosis, which is a rare, disabling, and potentially fatal systemic disorder that has been linked to exposure to gadolinium.[88]

During MRU, the collecting system, ureter, and bladder can be evaluated using either heavily T2-weighted sequences or T1-weighted sequences after intravenous administration of Gd-DTPA.[94,95,97-100] From a functional perspective, contrast-enhanced MRU techniques are designed primarily to reproduce the information that was provided with conventional diuretic renal scintigraphy, although protocols differ in regard to the timing of administration of furosemide and/or contrast material. One of the earlier MRU protocols[91,95,97,98,100,101] begins with non-enhanced spin-echo T1 and fat-suppressed, fast-spin-echo T2-weighted images of the kidneys, ureters, and bladder in coronal and axial planes. Gd-DTPA is then given by bolus intravenous infusion, after which a dynamic volumetric gradient-echo technique is used to continuously survey the entire urinary tract for 3 minutes, generating a series of 15-second images that can be displayed as a cine loop. The volume acquisition is then repeated at 1-minute intervals for 17 minutes, after which furosemide is given intravenously, and the imaging is repeated for an additional 15 minutes at 1-minute intervals. This "F+20" technique takes so long that sedated children frequently awaken before the examination can be completed. In addition, image quality is often degraded early during the excretion phase by magnetic susceptibility artifacts that result from the very high concentration of contrast material in the collecting system. Moreover, although plots displaying signal intensity versus time with this technique do graphically demonstrate delayed excretion in obstructed systems, they cannot be used to quantify washout from the collecting system and ureters, because the signal intensity does not follow a linear relationship at higher gadolinium concentrations.

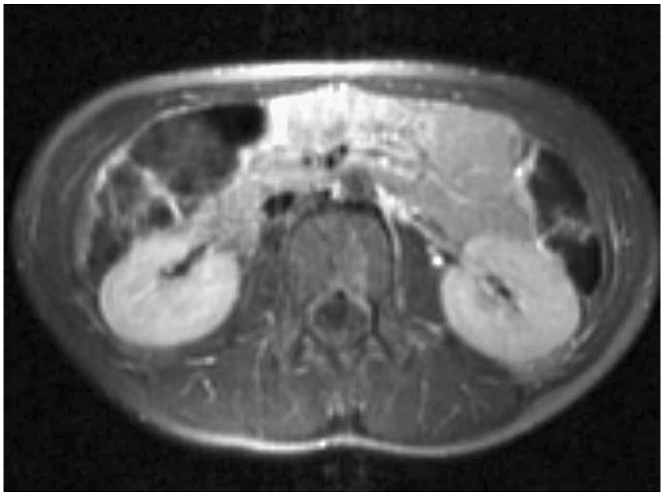

Figure 5-33 Normal T1-weighted (fat-suppressed) contrast-enhanced axial magnetic resonance image of the kidneys in a young child shows nearly homogeneous enhancement of the renal parenchyma diffusely.

Because of these limitations of the "F+20" MRU technique, the "F-15" protocol[95] was developed, in which furosemide is given 15 minutes before the contrast material, rather than afterward. Non-enhanced T1- and T2-weighted images

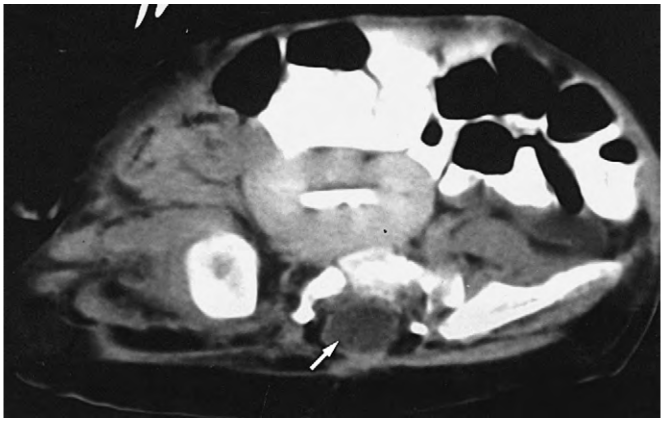

Figure 5-34 Right pelvic kidney in a 1-year-old boy with sacral anomalies and high imperforate anus. Contrast-enhanced axis computed tomographic (CT) image through the pelvis at the level of the sacroiliac joints shows the right kidney lying transversely, immediately anterior to the upper sacrum. The sacrum is dysraphic *(arrow)*.

are obtained in coronal and axial planes during the first 15 minutes after furosemide administration. Dynamic imaging is begun immediately after injection of the contrast material. Imaging time is dramatically shortened, and gadolinium-related magnetic susceptibility artifacts are eliminated. In addition, it is possible with this technique to quantitatively track the passage of contrast material from its appearance in the calyces to the renal pelvis and into the ureter. As a result, the diagnosis of obstruction can be based on functional asymmetries in excretion rather than solely on morphologic abnormalities. Differential renal function can also be calculated before the contrast material appears in the collecting systems, based on the volume of enhancing renal parenchyma during the corticomedullary phase. In the future, time-activity analysis of corticomedullary gadolinium transit will likely provide more precise assessments of differential function than is possible with current methods that rely on morphologic assessments of functioning renal parenchymal volume alone.

Non-enhanced MRU is performed without gadolinium and relies on the bright signal intensity from static fluid in the collecting systems on heavily T2-weighted sequences.[94,95,98,99,101,102] The signal intensity in the renal parenchyma is normally relatively suppressed because of its shorter T2 relaxation time. A series of single-shot fast-spin-echo sequences are performed with half-Fourier acquisitions and reconstructed as multiple images of variable thickness. In adults, steady-state free precession sequences are also becoming more popular. In patients with dilated collecting systems, non-enhanced T2-weighted MRU provides excellent visualization of the urinary tract. This technique is also very useful in patients who have impaired renal function, because the imaging relies solely on the physical characteristics of urine rather than on the excretion of contrast material by the kidney. The most important limitation of this technique is that it provides no direct functional information. As a result, it is most useful when used in combination with contrast-enhanced MRU. It is also limited by inability to evaluate nondilated systems, although visualization of nondilated collecting systems and ureters can be improved in some patients by administration of furosemide. Fluid-filled bowel loops and gallbladder can also be a problem if they are confused for urinary structures. Visualization of urinary calculi is limited on both conventional MRI and MRU, because they appear as filling defects or signal voids.

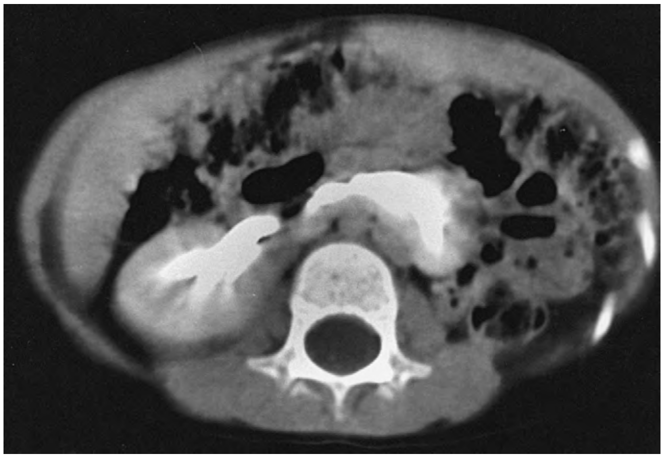

Figure 5-35 Left cross-fused renal ectopia. The left kidney overlies the spine, near the midline, in the lower abdomen. The left collecting system is directed toward the right side across the midline, and its lower pole is fused to the inferior hilar lip of the right kidney.

Magnetic Resonance Angiography

The inherent sensitivity of MRI to motion of blood within vessels allows for both quantitative and qualitative assessment of flow.[92,94,103,104] Ironically, early in the development of MRI, considerable effort was directed at eliminating the intravascular signal changes related to flow, because they were originally considered to be unwanted artifacts. However, the diagnostic importance of these flow-related signal changes was quickly recognized, leading to the development of magnetic resonance angiographic (MRA) imaging protocols that permit precise definition of vascular morphology and quantification of flow. Signal dropout from turbulent blood flow and degradation of image quality secondary to respiratory motion and saturation of in-plane blood flow on non-enhanced, flow-sensitive techniques such as phased-contrast MRA and time-of-flight MRA have some limitations in regard to the visualization of small vascular structures that can be particularly problematic in infants and smaller children. However, these limitations can be overcome on gadolinium-enhanced MRA by acquiring a three-dimensional data set within a single breath-hold. Continuing improvements in MRA technique in the future are likely to dramatically reduce the necessity of contrast-enhanced techniques such as CT angiography or conventional catheter angiography that utilize ionizing radiation.

CLINICAL PEDIATRIC GENITOURINARY APPLICATIONS OF COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Renal Anomalies

Most renal malformations, including renal agenesis, renal ectopia (Figs. 5-34 and 5-35), congenital obstructive uropathy, multicystic dysplastic kidney, and complicated duplication anomalies (Figs. 5-36 and 5-37), are primarily evaluated with US and renal scintigraphy. The role of CT or MRI is limited to more complicated situations in which one or both of these modalities can provide clinically useful information that cannot be obtained noninvasively by other means. Imaging in the axial plane with either CT or MRI is usually satisfactory. Direct coronal imaging with MRI permits rapid evaluation of large portions of the abdomen and pelvis at one time, which can be particularly useful when searching for small, poorly functioning

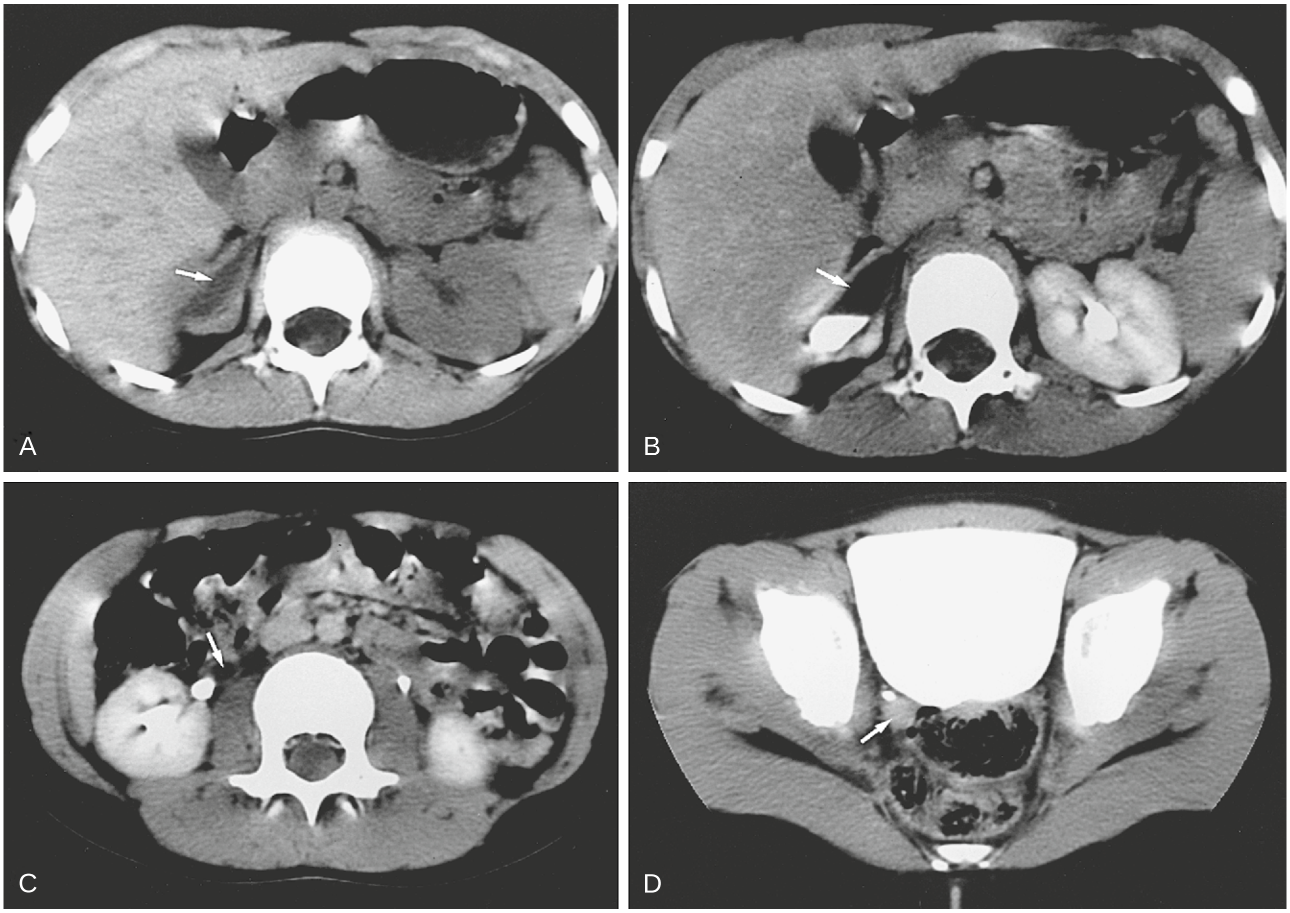

Figure 5-36 Complete right duplex kidney with an extravesical ectopic right upper-pole ureter in a 7-year-old girl with persistent incontinence. **A,** Non-enhanced axial computed tomographic (CT) image through the upper poles of the kidneys. There is a distended, slitlike, right upper-pole calyx *(arrow)*. There is minimal surrounding upper-pole parenchyma. **B,** Contrast-enhanced axial CT image through the upper poles of the kidney. There is now a contrast agent–urine level in the right upper pole calyx, with the contrast material layering dependently *(arrow)*. **C,** Contrast-enhanced axial CT image through the right renal hilum. The lower-pole collecting system and proximal lower-pole ureter are densely opacified. The right upper-pole ureter *(arrow)*, containing nonopacified urine, lies anterior and medial to the lower-pole ureter. **D,** Contrast-enhanced delayed axial CT image through the pelvis, obtained 20 minutes after contrast agent administration. The distal upper-pole ureter *(arrow)* is now becoming faintly opacified and lies posterior and medial to the lower-pole ureter, which is densely opacified.

kidneys. On the other hand, the site of fusion in horseshoe kidney or crossed-fused ectopia is often better visualized on axial images (see Fig. 5-35).

In girls, unilateral renal agenesis can be associated with uterovaginal anomalies, such as agenesis, duplication, and atresia.[105] In boys, unilateral agenesis can be associated with an ipsilateral seminal vesicle cyst.[106] Rarely, the ipsilateral vas deferens and testis are also absent. CT or MRI occasionally reveals a tiny, poorly functioning or nonfunctioning kidney in a child who appears on US, IVU, or renal scintigraphy to have unilateral renal agenesis. In such cases, the small kidney most likely represents the remnant of an involuted multicystic dysplastic kidney, and a single ectopic ureter is frequently present.[107] In the absence of associated lower genitourinary anomalies, definitive historical information, or previous imaging studies, however, it is not possible to differentiate this from other causes of severe renal atrophy, such as renal infarction or reflux nephropathy, on the basis of imaging alone.

The history of incontinence in a girl that is characterized by persistent and incessant dampness is suggestive of an extravesical, ectopic ureter that inserts into the urethra or vagina or onto the perineum. Although the ectopic ureter usually drains the upper pole of a completely duplicated collecting system,[108] incontinence can also occur with a nonduplicated ureter that drains through an ectopic orifice.[109] Boys who have this anomaly are not incontinent, because the ectopic ureter always inserts proximal to the urethral sphincter.[110] Because the upper pole that is drained by an ectopic ureter is not always dilated, it may not be visible on US, and the findings can similarly be very subtle on IVU, particularly if the offending upper pole does not function well enough to be directly visualized.[111] If the ectopic ureter drains a nonduplicated collecting system, the affected kidney is often very small and dysplastic, with very poor function. CT with thin sections through the kidneys obtained 10 to 15 minutes after administration of contrast material (see Fig. 5-36), coronal T1-weighted MRI, and MRU are the most sensitive modalities for diagnosing this disorder and should be performed in any girl who presents with a history of incontinence suggestive of an occult ectopic ureter.[108,109,112]

Renal Infections and Scarring

On enhanced CT imaging, acute pyelonephritis appears as wedge-shaped or triangular areas of decreased enhancement within the renal parenchyma.[113-115] Pyelonephritis is

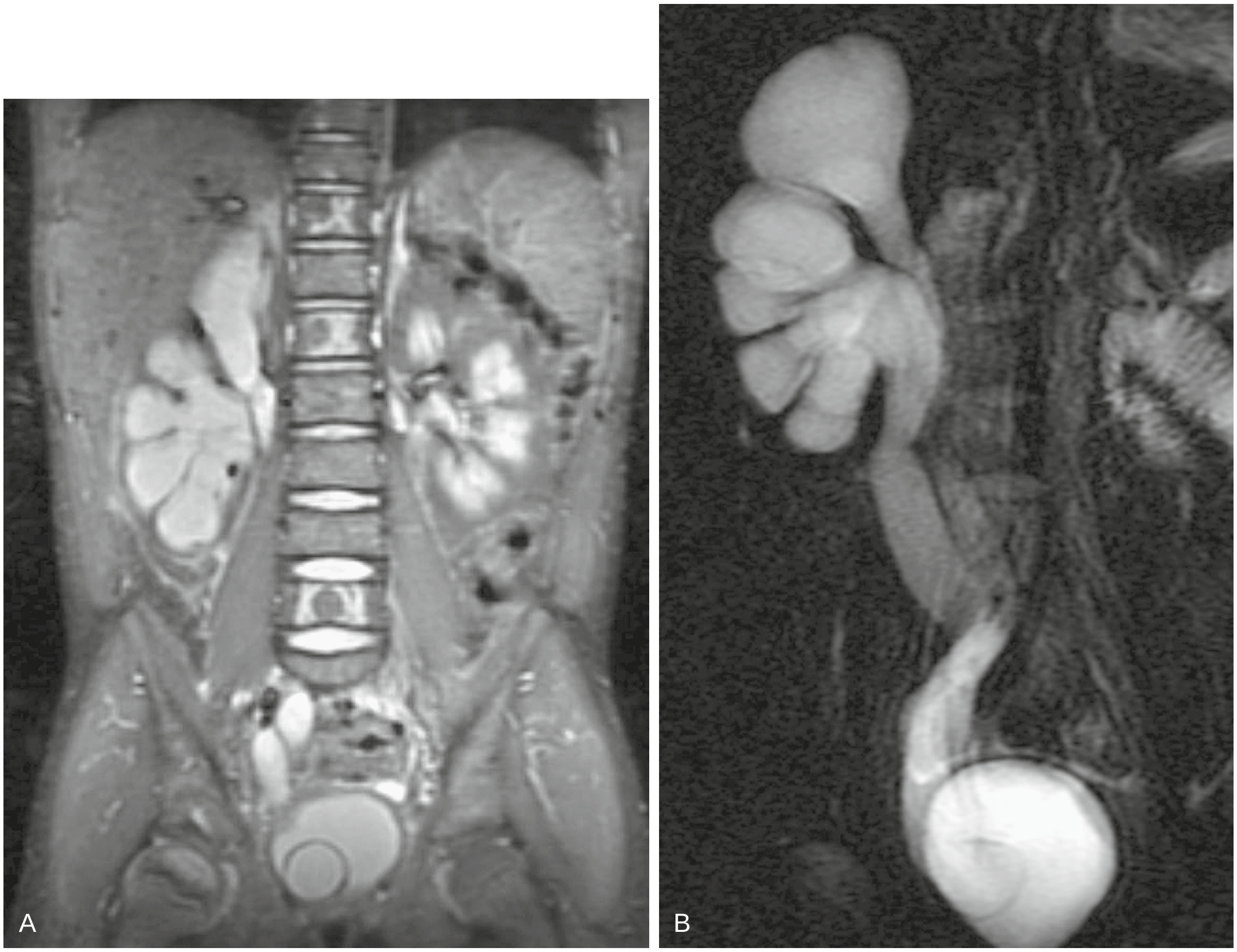

Figure 5-37 Magnetic resonance urogram (MRU) in a 6-year-old boy with sickle cell disease and a complete right duplex kidney with right upper-pole hydroureteronephrosis and ureterocele. **A,** Coronal T1-weighted contrast-enhanced MRU clearly illustrates the duplicated right collecting system and the obstructed upper-pole hydroureter ending in a ureterocele. The signal changes in the lumbar spine are related to the patient's hemoglobinopathy. **B,** Coronal thick-slab re-projection from non–contrast-enhanced T2-weighted MRU very elegantly displays the anatomy of the duplicated right kidney and the two intertwined right ureters with the upper-pole ureter ending in a ureterocele.

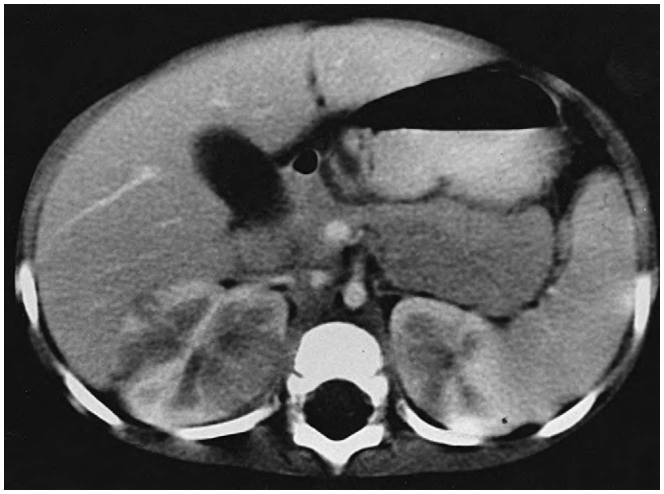

Figure 5-38 Bilateral acute multifocal pyelonephritis in a 6-month-old girl with fever and bacteriuria. Contrast-enhanced axial CT image through the upper poles of the kidneys. Multiple segmental, low-attenuation zones of reduced perfusion and enhancement are visible bilaterally. Some of the affected areas have a faintly striated appearance.

characteristically segmental in distribution and occurs more often in the renal poles (Fig. 5-38). The affected areas appear edematous, with convex, rounded margins, and can produce bulges in the renal contour that can mimic intrarenal masses. If large portions of the kidney are involved, the kidney appears globally enlarged, with patchy enhancement of the less involved areas. The diagnosis of acute pyelonephritis is difficult on non-enhanced CT, because infected segments are generally isodense or only slightly hypodense in relation to adjacent normal parenchyma. Increased attenuation in acute pyelonephritis on non-enhanced CT suggests localized hemorrhage secondary to segmental venous obstruction. The abnormal pattern of enhancement of the infected areas can persist for up to several months after completion of antibiotic therapy before resolving or progressing to scar formation.

MRI techniques for the diagnosis of acute pyelonephritis and renal cortical scarring have been investigated both in piglets and in humans.[92,116-119] On enhanced fast-spin-echo T2-weighted and inversion recovery MRI sequences, shortening of the T1 and T2 relaxation times by gadolinium results in marked reduction in signal intensity in normally enhancing renal parenchyma (Fig. 5-39). By comparison, in acute pyelonephritis, the signal intensity remains very bright in non-enhancing, infected segments where the gadolinium

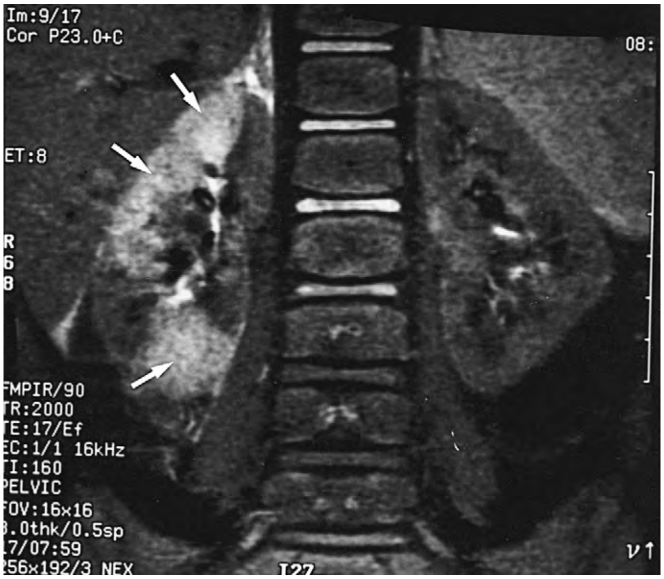

Figure 5-39 Right acute multifocal pyelonephritis. Gadolinium-enhanced, coronal inversion recovery image through the kidneys. Multiple segmental zones of abnormally increased signal are visible throughout the right kidney *(arrows)*. The left kidney appears normal. (Courtesy of Drs. Lonergan and Pennington. From Lonergan GJ, Pennington DJ, Morrison JC, et al: Childhood pyelonephritis: comparison of gadolinium-enhanced MR imaging and renal cortical scintigraphy for diagnosis. *Radiology.* 1998;207:377-384.)

concentration is much lower. Infected renal segments are also typically edematous, and perinephric edema is common. Small amounts of perinephric fluid are more often visible on MRI than on CT in patients with pyelonephritis but do not necessarily indicate the presence of a perinephric abscess that requires drainage.[91,92] Cortical scars from previous acute pyelonephritis episodes appear on MRI as areas of parenchymal loss that do not change in signal intensity between enhanced and non-enhanced inversion recovery sequences. The sensitivity of fat-saturated T1-weighted imaging in combination with an enhanced inversion recovery sequence is comparable to that of DMSA renal cortical scintigraphy in detecting acute and chronic pyelonephritis and provides far superior anatomic resolution.

In children with cortical scarring and atrophy after pyelonephritis, MRI reveals areas of parenchymal loss that do not change in signal intensity between pre- and post-gadolinium inversion recovery sequences.[91,116,118-120] Retraction of the renal contour leads to loss of renal parenchymal volume as the scar matures. MRI is as sensitive as DMSA renal cortical scintigraphy in detecting renal scarring and provides far superior anatomic resolution.

Renal abscesses and other serious acute complications of pyelonephritis are very rare in otherwise healthy children who develop acute ascending pyelonephritis.[114,115] Although such complications have traditionally been evaluated with CT, which demonstrates both the intrarenal and the extrarenal extent of the infectious process,[115,121] MRI is likely to be used with increasing frequency because it allows direct multiplanar imaging and superior tissue contrast (Fig. 5-40). Abscesses can be intraparenchymal or perirenal; they demonstrate an enhancing wall surrounding a central, low-density, nonenhancing cystic area. The distinction between uncomplicated acute pyelonephritis and abscess is important, because the former is treated with antibiotics alone, whereas an abscess may require drainage.

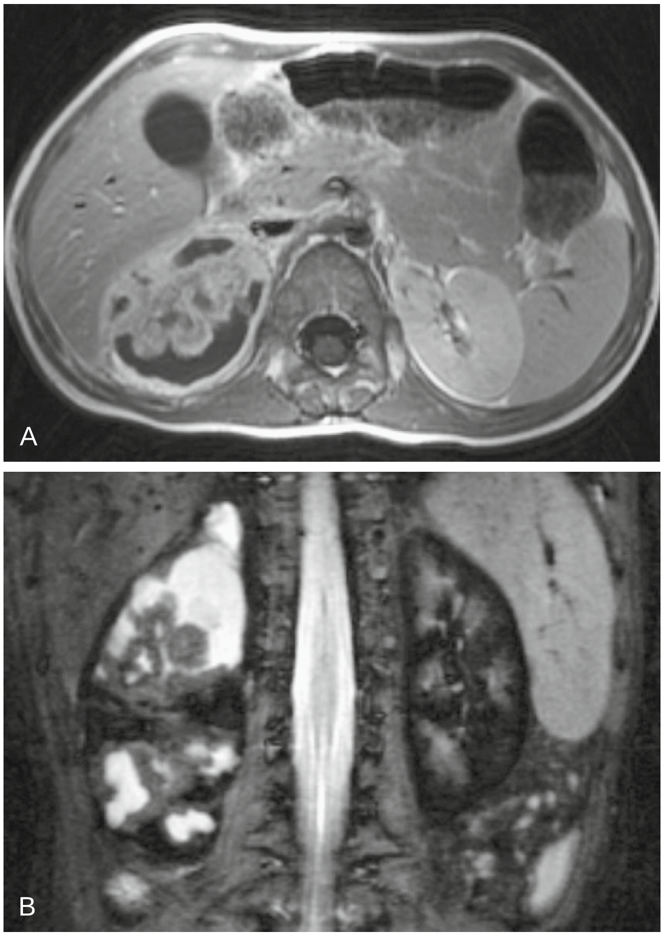

Figure 5-40 Severe right pyelonephritis with perinephric and multiple intraparenchymal abscesses in a 3-year-old boy with fever and gross hematuria. **A,** Axial postcontrast, T1-weighted (fat-suppressed) magnetic resonance image (MRI) through the upper pole of the right kidney shows irregular shape and attenuation of the upper pole, with a multiple, irregular, intraparenchymal abscess with enhancing walls anteriorly and a larger perinephric abscess surrounding the posterior aspect of the upper pole of the right kidney, which also has an enhancing wall. **B,** Coronal postcontrast fast-spin-echo inversion recovery MRI of the kidneys shows extensive abnormal signal throughout the right kidney, with multiple very-high-signal-intensity, focal, fluid-filled cavities in the lower pole and a large perinephric collection surrounding the upper pole. Bright signal superior to the right kidney most likely represents adrenal hemorrhage.

Diffusion-weighted MRI provides information on velocity and direction of movement of water molecules in tissue under the influence of a diffusion gradient. Differences in the relative mobility or viscosity of water molecules in tissues create the contrast in diffusion-weighted imaging.[122] Until recently, application of diffusion-weighted imaging techniques outside the central nervous system has been severely limited by respiratory and cardiac motion. Recent development of ultrafast, single-shot echo planar imaging techniques now permit its application elsewhere, including in the urinary tract. Marked hyperintensity on diffusion-weighted sequences in pyelonephritis and renal abscess is believed to result primarily from cytotoxic edema and intratubular inspissation of inflammatory cells.[123,124] Because pus is a thick, high-viscosity fluid consisting of water, inflammatory cells, necrotic tissue, and proteinaceous exudates, water proton mobility is very restricted, both in renal abscess and in a pyonephrotic

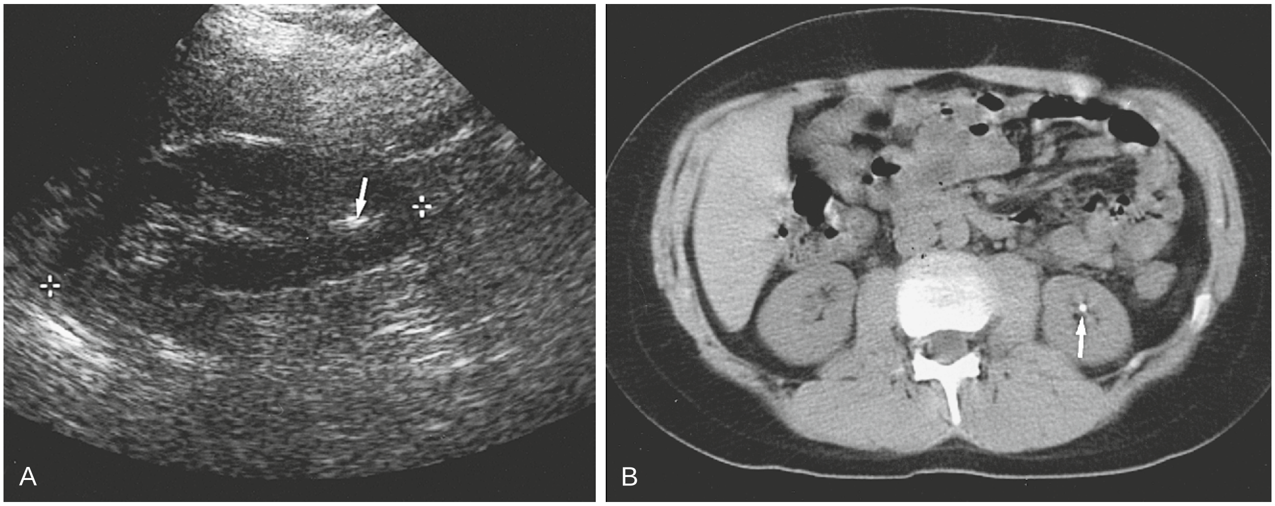

Figure 5-41 Computed tomographic (CT) confirmation of a nonshadowing left lower-pole calculus in a 7-year-old boy with oxalosis. **A,** Ultrasonographic longitudinal coronal view of the left kidney. There is a 5-mm nonshadowing echogenic focus in the lower pole *(arrow)*. **B,** Non-enhanced axial CT image through the lower poles of the kidneys. There is a 5-mm brightly echogenic calculus in the left lower pole *(arrow).*

collecting system, resulting in a very low apparent diffusion coefficient (ADC) with very high signal intensity on diffusion-weighted images and relative signal hypointensity of ADC maps. Acute or subacute hemorrhage within the collecting system or a renal cyst can also produce high signal intensity on diffusion-weighted sequences and can potentially mimic purulent material.

Nephrolithiasis

Non–contrast-enhanced CT has almost completely replaced IVU for the investigation of suspected urolithiasis.[125-127] Noncontrast CT can be performed rapidly and is relatively easy to interpret and highly accurate, with excellent interobserver and intra-observer agreement in interpretation.[128] Neither oral nor intravenous contrast material is given. In fact, the presence of either type of agent interferes with proper interpretation. Contiguous 4- to 5-mm thick axial images are obtained from the top of the kidneys to the symphysis pubis during a single breath-hold. In very tall individuals, a second acquisition may be necessary through the patient's pelvis. The diagnosis of a ureteral calculus is based principally on direct identification of the offending calculus within the ureter. Associated findings, such as edema of ureteral wall (the "tissue rim sign") and of the fat surrounding the ureter at the level of the impacted stone, suggest the presence of a localized inflammatory reaction to the calculus.[129-131] Similarly, edema of the ureterovesical junction can be seen with calculi that are impacted within the submucosal tunnel. Hydronephrosis and ureteral dilatation proximal to the stone are highly predictive of an obstructing calculus, particularly when they are associated with other findings, such as perinephric stranding. Transient persistence of any or all of these findings after passage of a previously impacted stone occasionally provides an indirect clue to the correct diagnosis.

Abdominal radiography and US are generally preferred for the diagnosis of renal calculi. However, non–contrast-enhanced CT can be very helpful in patients whose kidneys are difficult to examine satisfactorily with US. For example, in older patients with myelomeningocele or spinal cord injuries, sonographic visualization of the kidneys can be hampered by severe scoliosis or interfering bowel gas. Multiple small calculi in ectopic kidneys, horseshoe kidneys, or severely hydronephrotic kidneys can be precisely localized with CT. Small calculi that fail to shadow at sonography are also readily identified at CT (Fig. 5-41).

Wilms' Tumor

US is usually the first imaging study performed in an infant or young child who presents with a palpable abdominal mass; it is, therefore, the modality by which the diagnosis of Wilms' tumor is initially made in most cases. On US, Wilms' tumor appears as a predominantly solid, hyperechoic, intrarenal mass. The remaining normal renal parenchyma is often visible splayed around the periphery of the mass. The mass is often large and can contain cystic necrosis and hemorrhage.

On CT, Wilms' tumor appears as a low-attenuation renal mass on non-enhanced scans.[132] Calcification is uncommon. Postcontrast scans show a more inhomogeneous appearance of the mass, with variable enhancement of the solid components and lack of enhancement in areas of necrosis and cystic change (Fig. 5-42). On MRI, the signal intensity in the mass is typically inhomogeneous, with predominantly low signal intensity on T1-weighted sequences and bright signal on T2-weighted sequences. Solid areas enhance after administration of gadolinium.[133,134] CT and MRI generally provide comparable information regarding local tumor extent and regional adenopathy, and both are superior to US with regard to precisely defining tumor extent and staging. However, direct multiplanar imaging with MRI occasionally provides more detailed information in cases where direct invasion of adjacent structures is difficult to confirm or exclude at CT. Careful evaluation of the contralateral kidney for tumor or nephroblastomatosis is essential. Because of the propensity of Wilms' tumor to grow into the renal vein and inferior vena cava, these structures should be carefully evaluated for evidence of tumor thrombus. Identification of the cranial extent of the thrombus is critical in presurgical planning.[135,136]

Renal Trauma

CT is the principal modality used for the evaluation of patients with suspected renal trauma. CT provides both anatomic and functional information and is superior to US in the evaluation

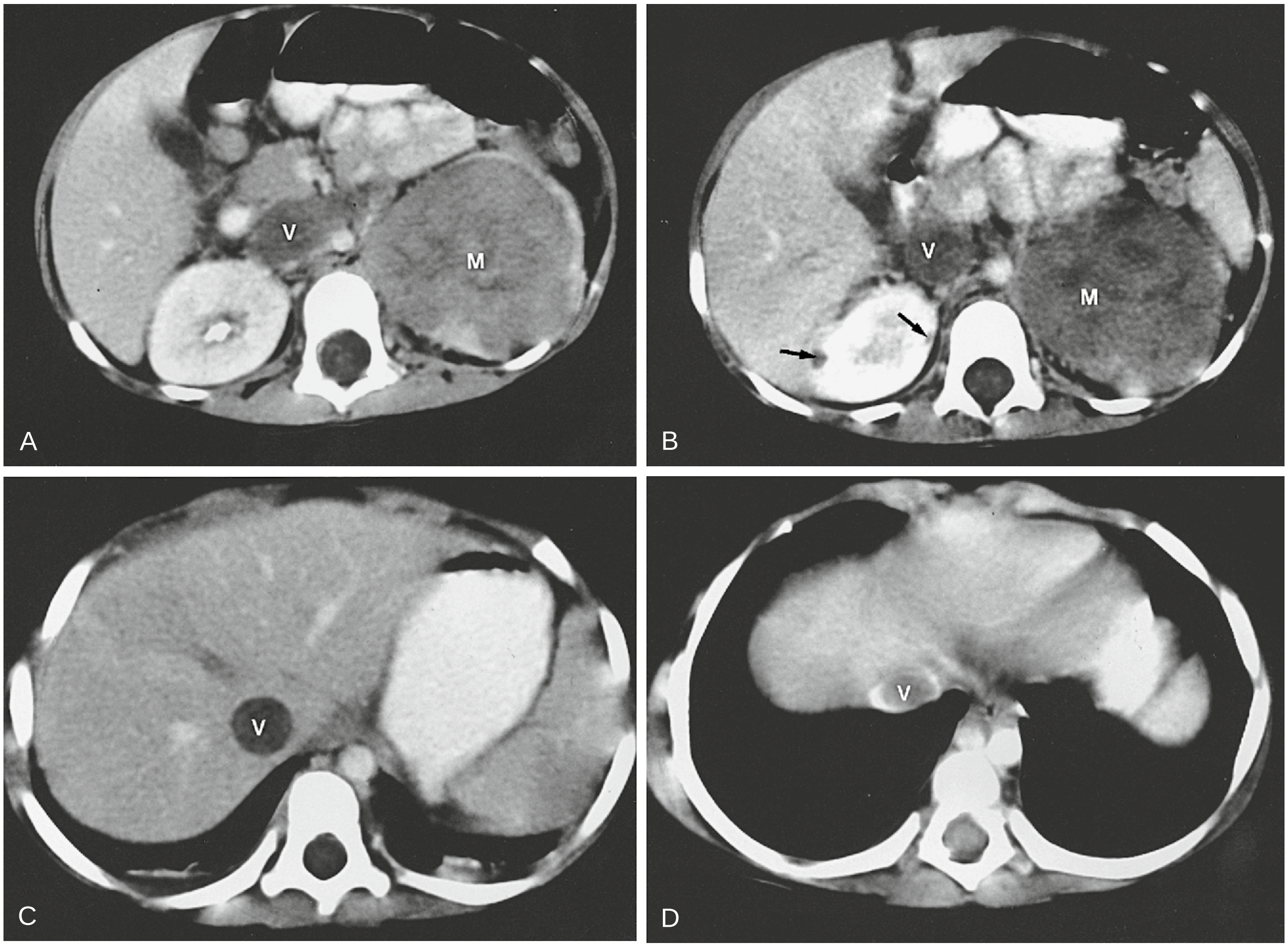

Figure 5-42 Left Wilms' tumor with extension into the left renal vein and inferior vena cava and contralateral nephroblastomatosis in a 4-year-old girl. **A,** Contrast-enhanced axial computed tomographic (CT) image through the kidneys at the left of the left renal vein. There is a large, low-attenuation, solid left renal mass (M). The left renal vein (V) and inferior vena cava are markedly distended by non-enhancing, low-attenuation tumor thrombus. **B,** Contrast-enhanced axial CT image through the upper poles of the kidneys. There is a large, low-attenuation, solid left renal mass (M). The inferior vena cava (V) is distended by non-enhancing, low-attenuation tumor thrombus. In addition, there are two small, non-enhancing peripheral nodules *(black arrows)* in the upper pole of the right kidney, consistent with perilobar nephrogenic rests. **C,** Contrast-enhanced axial CT image through the liver. The intrahepatic inferior vena cava (V) is distended with non-enhancing tumor thrombus. **D,** Contrast-enhanced axial CT image through the dome of the liver. The tumor thrombus within the inferior vena cava (V) extends to its junction with the right atrium.

of patients who have traumatic renal injuries. With CT, the entire abdomen and pelvis can be readily evaluated, permitting immediate diagnosis of associated injuries to other viscera. CT diagnoses also correlate very closely with surgical findings.[137,138]

Renal injuries range from isolated parenchymal contusions without subcapsular or perirenal hemorrhage (grade I), to superficial parenchymal lacerations not involving the collecting system (grade II), to deeper parenchymal lacerations associated with urinary extravasation (grade III), to extensive disruption and fragmentation of the kidney (grade IV). Grades I and II account for more than half of all injuries in children.[137,138] Function is typically reduced or absent in the area of the injury, secondary to venous thrombosis and vascular compression by adjacent edematous parenchyma or clot. Function frequently returns with healing. However, in patients with extensive fractures, infarction of completely devascularized renal fragments is not associated with recovery of function.

Subcapsular and perirenal hemorrhage frequently accompanies both superficial and deeper parenchymal lacerations.[138,139] Subcapsular collections closely conform to the renal contour and are separated from Gerota's fascia by the perirenal fat. Perirenal blood extends to Gerota's fascia. On precontrast images that are performed soon after the injury, blood surrounding the kidney appears somewhat higher in attenuation than the adjacent renal parenchyma. After administration of contrast material, this relationship is reversed, with the renal parenchyma enhancing and the adjacent, non-enhancing clot appearing relatively lower in attenuation. With time, as the clot matures and liquefies, its attenuation decreases. Urinomas occur as the result of disruption of the collecting system and appear as masses of fluid attenuation. If the leakage is still active during the study, the mass will contain opacified urine and the site of the extravasation from the collecting system occasionally can be directly documented (Fig. 5-43).

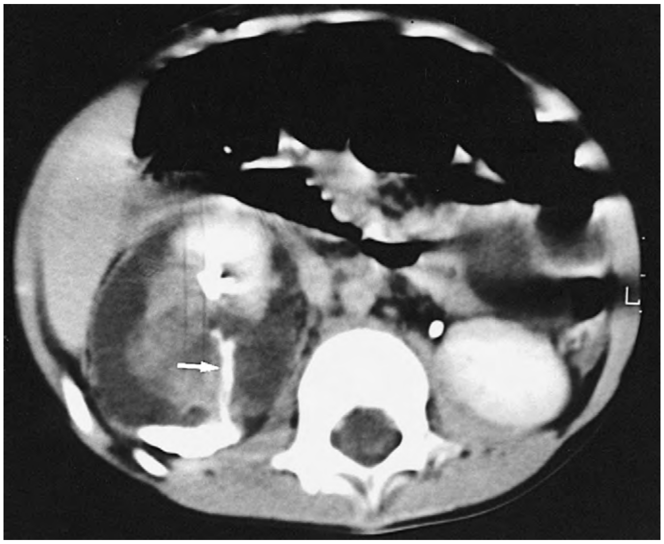

Figure 5-43 Right renal fracture and lower-pole infarction with laceration of the collecting system in a 4-year-old boy. Contrast-enhanced axial computed tomographic image through the lower poles of the kidneys. The cortical contour and shape of the right kidney are markedly distorted, with no enhancement of the parenchyma in the posterior portion of the lower pole. There is a large right perirenal fluid collection with contrast material *(arrow)* extravasating from the lacerated collecting system and layering dependently in the fluid collection posteriorly.

Complete loss of flow and function in the kidney is suggestive of an injury to the renal vascular pedicle and is one of the few absolute indications for emergent surgical intervention. A rim of enhancement at the periphery of the kidney is frequently present secondary to collateral flow through capsular vessels.[140,141] Severe or complete renal vascular compromise can result from subendothelial hemorrhage or dissection within the wall of the renal artery, from direct laceration of the vessel, or from extrinsic compression of the renal vascular pedicle by adjacent hematoma in the perirenal space.

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CHAPTER 6

ENDOSCOPY OF THE LOWER URINARY TRACT

Ranjiv Mathews

Endoscopy of the lower urinary tract has been performed in infants and children; however, the potential for therapeutic intervention was limited by the size of available instrumentation. Recent advances in the miniaturization of instruments and video technology allow all but the smallest infants to be examined and treated endoscopically if indicated.[1,2] Further extension of this technology has even permitted fetal endoscopic diagnosis and, more recently, intervention (see later discussion).

Most infants and children require anesthesia for performance of endoscopy. In the male, meatotomy may be necessary for introduction of larger instruments and, if indicated, should be performed before meatal injury occurs.[3] Perineal urethrostomy has been performed in the past for access to the proximal urethra; however, most cases today can be performed without this added intervention.

This chapter addresses endoscopy of the lower urinary tract (cystourethroscopy and antegrade endoscopy).

TECHNIQUES AND INSTRUMENTATION

A cystoscopic suite that permits fluoroscopic or ultrasonographic visualization is the ideal working environment for pediatric diagnostic and therapeutic endoscopy. In infants, an open-leg posture using padded extension boards from the table is recommended. The older child can be placed in a standard lithotomy position for lower tract endoscopy. Irrigating fluids (sterile normal saline or water) are warmed to body temperature to prevent potential hypothermia during endoscopy. Normal saline solution is used in most instances to prevent significant fluid absorption. If the patient has spina bifida, exstrophy, or other major congenital anomaly with potential for latex allergy, appropriate precautions are used as indicated. Additionally, children who have myelodysplasia with significant contractures, or spinal fusion, should have their extremities and back padded well to prevent injury and the development of pressure ulcers.

Endoscopic evaluations should commence with careful examination of the external genitalia to identify labial adhesions, ectopic ureters, or other morphologic anomalies that may require management. The width of the urethral meatus should be evaluated to determine whether trauma is likely to result from the cystoscope chosen for the procedure. Patients being evaluated for genital ambiguity and those with concerns for voiding dysfunction may also have a careful rectal examination performed at the time of cystoscopic evaluation.

Pediatric versions of cystoscopes are now available from most manufacturers. Larger scopes use the Hopkins rod-lens system (Fig. 6-1). The newer, thinner, multifunction scopes have fiberoptic systems that permit visualization while providing an adequate working channel for instrumentation. Use of a video camera system allows magnification and improved visualization while permitting recording of procedures for teaching or comparison with follow-up studies. Although the cystoscopes shown are the ones I prefer, a variety of excellent instruments with similar characteristics are available from various manufacturers. It is important to have a selection of cystoscopes available for use during procedures. Most endoscopes available today can be used for multiple functions. Cystoscopy, ureteroscopy, and nephroscopy can all be accomplished with currently available multifunction pediatric endoscopes.

Cystoscopes

Routine cystoscopic evaluation for diagnosis can be performed with a 5F (1.65-mm) cystoscope (Fig. 6-2). This permits excellent visualization with minimal trauma to the urethra. Most 5F cystoscopes are one-piece units with a 2.5F (0.83-mm) or 3F (0.99-mm) working port. This limits their therapeutic utility to the insertion of guidewires or removal of stents or small calculi. The 7F (2.31-mm) or larger cystoscopes provide a 5F working channel that allows many pediatric instruments to be inserted. Cystoscopes with an offset lens allow a straight path for the working channel (Fig. 6-3). Flexible cystoureteroscopes are also available for pediatric applications. Most are 7.5F (2.48 mm) in diameter and provide a 3.6F (1.19-mm) working channel for instrumentation (Fig. 6-4).

Resectoscopes

Rigid resectoscopes have similar setup to their adult counterparts. A variety of loops and cautery ends have been developed. In addition, hooked and straight blades for cold knife incision are available. Most use the Hopkins rod-lens system, but fiberoptic systems are also becoming available.

Fetal Endoscopes

Improvements in microendoscopy have allowed diagnosis and, more recently, therapy in the fetus. The fetal eyes appear to have natural protection against injury from the high-intensity light used during in utero–endoscopy.[4] The most frequently used application of fetal endoscopy has been laser coagulation of aberrant vessels in monochorionic twins with twin-twin transfusion syndrome.[5]

This technology has increasingly been applied to the antenatal management of urologic abnormalities. Fetal endoscopes used to date have a diameter of 1.3 mm. Diagnosis of urethral obstruction can be made, and the technology has been extended to management. Ablation of posterior urethral valves has been performed with either a saline flush technique or guidewire insertion.[6] Antegrade valve ablation has also been described.[7]

Working Instruments

Graspers, both flexible and rigid, are available in sizes from 3F to 5F for applications through rigid and flexible scopes. Rigid graspers work well with the offset lens scopes. 3F and 5F Bugbee electrodes are also available for fulguration. Open-ended ureteral stents with a guidewire may also be modified to permit cauterization. The tip may be bent to form a coagulating hook. Recently, a 5F cutting electrode has been developed that has a retractable, angled tip for pediatric application (Fig. 6-5).

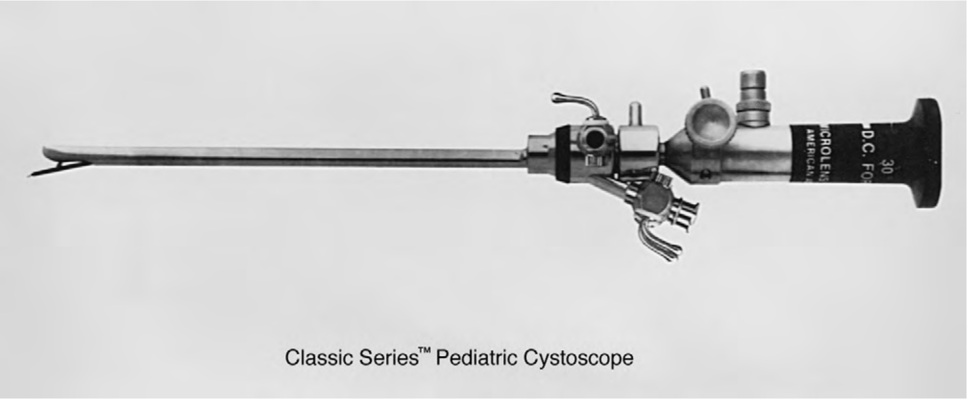
Classic Series™ Pediatric Cystoscope
MICROLENS AMERICAN
D.C. FO
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Figure 6-1 A 14.5F (4.79-mm) pediatric cystoscope with two working channels. (Courtesy of Circon Corporation.)

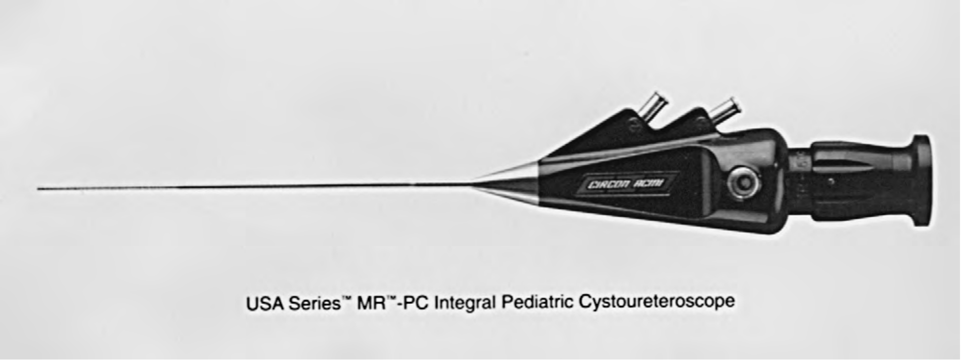
USA Series™ MR™-PC Integral Pediatric Cystoureteroscope
CIRCON ACMI

Figure 6-2 A 5F (1.65-mm) diagnostic cystoscope with a 3F (0.99-mm) working channel. (Courtesy of Circon Corporation.)

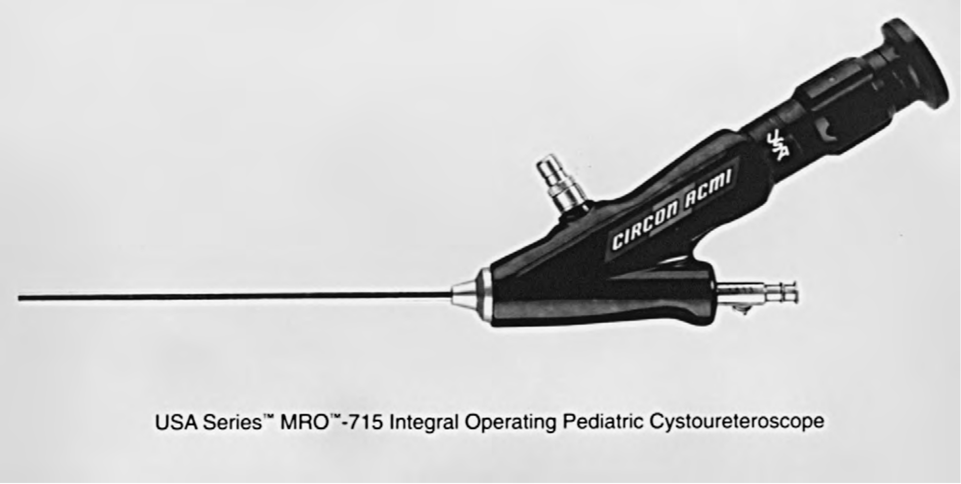
USA Series™ MRO™-715 Integral Operating Pediatric Cystoureteroscope
CIRCON ACMI
USA

Figure 6-3 A 7F (2.31-mm) integral cystoscope with an offset lens and a straight 5F (1.65-mm) working channel. (Courtesy of Circon Corporation.)

Electrohydraulic probes have been available for some time at 3F and 5F sizes. Ultrasonic probes have now been developed to work within a 5F channel. These devices have increased the armamentarium of equipment available for pediatric endoscopy.

ROLE OF ENDOSCOPY IN PEDIATRIC UROLOGY

Hematuria

Hematuria is commonly noted in the child, unlike the adult, but usually is not associated with neoplasia.[8] Causes for blood or urinary discoloration in the pediatric population include infections, medications, diet, and renal medical disease. Cystoscopy usually is not indicated. Urinalysis and culture and renal and bladder ultrasound studies should be performed. Some boys may present with hematuria, typically at the end of urination or as spots on the underwear. Endoscopic examination in these children is typically negative and is not indicated. Pathologic examination demonstrates squamous metaplasia.[9] Management is expectant with most children. Endoscopy is reserved for those with significant and protracted bleeding. In patients with a significant history of travel to endemic areas, a high degree of suspicion should be maintained for potential parasitic infections[10] that can manifest with hematuria (Fig. 6-6).

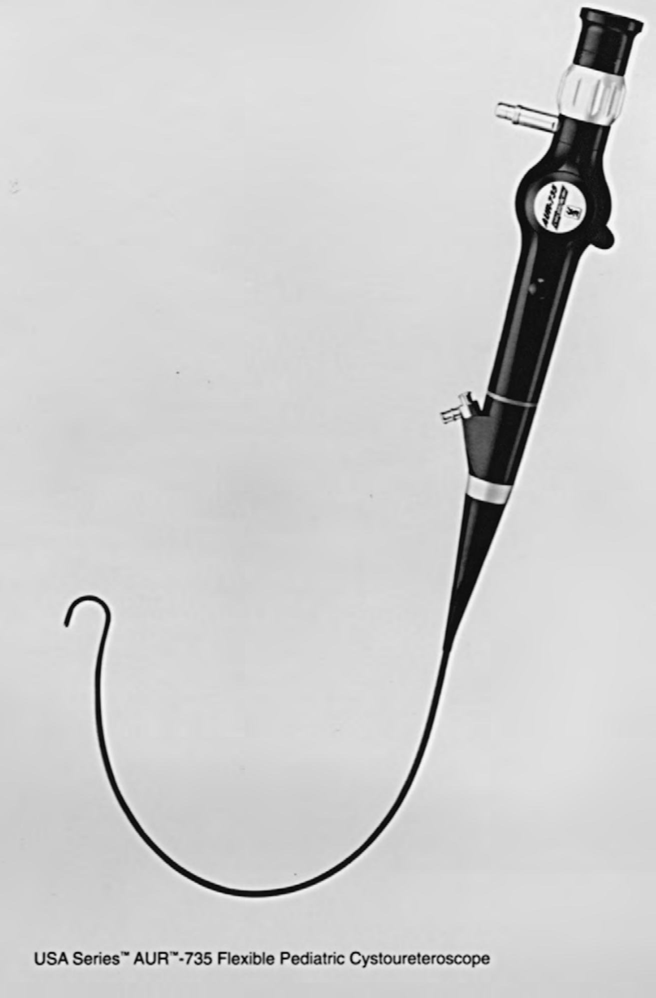

Figure 6-4 A 7.5F (2.48-mm) flexible pediatric cystoureteroscope. (Courtesy of Circon Corporation.)

Children who are undergoing chemotherapy for malignancies may develop hematuria secondary to medication toxicity or reduction in clotting factors.[11] Cystoscopic evacuation of blood and clot and bladder irrigation can provide relief of obstruction and promote mucosal healing. Fulguration and instillation of hemostatic agents may be required in some children to prevent ongoing blood loss.

Posterior Urethral Valves

The diagnosis of posterior urethral valves is usually suspected on antenatal ultrasonography. Postnatal confirmation of the diagnosis is made with voiding cystourethrography. Endoscopic incision of valves has considered the primary treatment modality when possible (Fig. 6-7).[2,12]

Once the patient is medically stable, endoscopic fulguration can be performed in all but the smallest infants. A 5F cystoscope with a 3F working channel can be inserted with minimal trauma and permits fulguration with the use of a coagulating Bugbee electrode. Alternatively, the Collings knife electrode of the resectoscope may be used for incision of the valves. Incision of the valves rather than aggressive ablation is recommended to prevent the later development of strictures.[13] Incision is typically performed at the 5 and 7 o'clock positions (Fig. 6-8). Incision may also be performed using a laser.[14] Urethral catheterization may be used for a few days after valve ablation.

In infants in whom a transurethral procedure is not possible due to urethral caliber, antegrade ablation has been performed. A 9.5F (2.14-mm) cystoscope is used in conjunction with a suprapubic sheath for incision of the valves at the anterior commissure.[12] Perineal urethrostomy is infrequently required for the incision of posterior urethral valves.

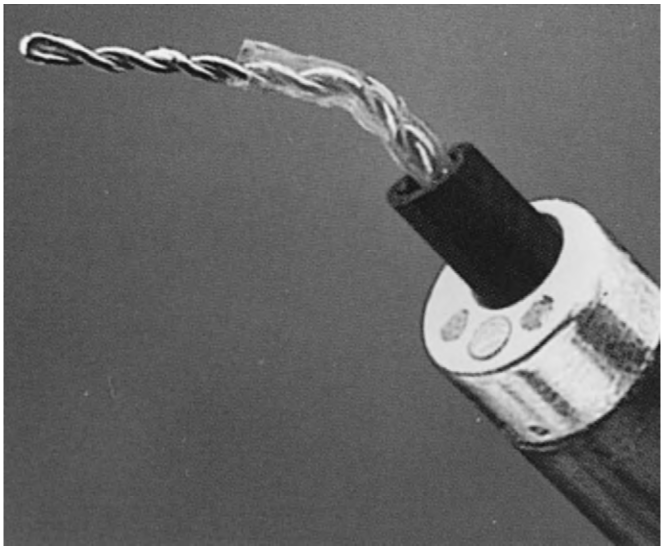

Figure 6-5 A 5F (1.65-mm) retractable angled electrocautery tip.

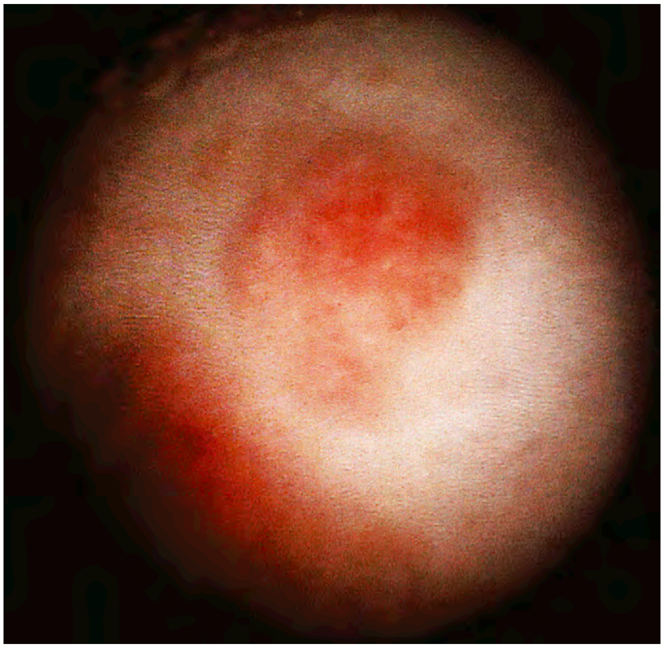

Figure 6-6 Schistosomiasis of the bladder in a 6-year-old boy.

Ureteroceles and Ureteral Ectopia

Ureteroceles are typically noted in girls in association with ureteral duplication anomalies (Fig. 6-9). Single-system ureteroceles may also be noted and are more frequent in boys. Endoscopy can differentiate intravesical (orthotopic) ureteroceles (Fig. 6-10) from those that are extravesical (ectopic).

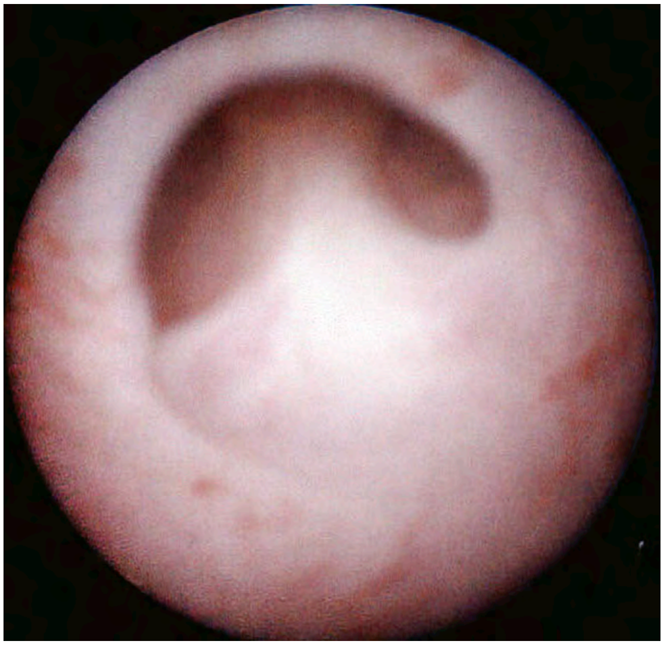

Figure 6-7 Posterior urethral valves extending from the verumontanum.

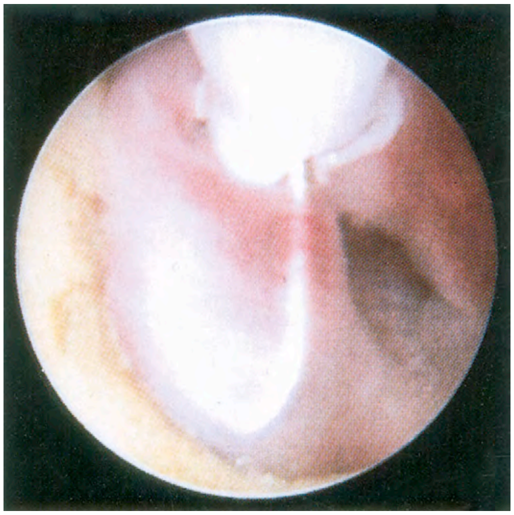

Figure 6-8 Valve leaflet engaged before incision. (Courtesy of Umesh Patil, MD.)

Early attempts at endoscopic management of ureteroceles were universally associated with the development of massive reflux. Monfort and colleagues were able to demonstrate that, with appropriate incision, reflux did not always result.[15] This procedure has now become the initial intervention in most infants with ureteroceles. Incision or puncture is performed as low as possible in the ureterocele within the bladder neck (Fig. 6-11A).[15,16] Entry into the ureterocele is identified by urine jetting from the incision. When a ureterocele has a component extending into the bladder neck, that component should be incised longitudinally to prevent urine from filling this segment and acting as an obstruction (see Fig. 6-11B).[17] Ureterocele incision can be performed with cautery or with the use of laser.

Puncture of the intravesical ureterocele is associated with high success rates, with minimal postprocedure reflux or need for later surgery. Children with ectopic ureteroceles, however, do not appear to fare as well with incision, as reflected by a greater need for later curative surgery.[18,19] Postprocedure reflux is noted in 30% to 47% of children treated with incision.[20,21] Incising the ureterocele parallel to the bladder wall causes the decompressed wall of the ureterocele to act as a flap valve, preventing reflux.[1,17]

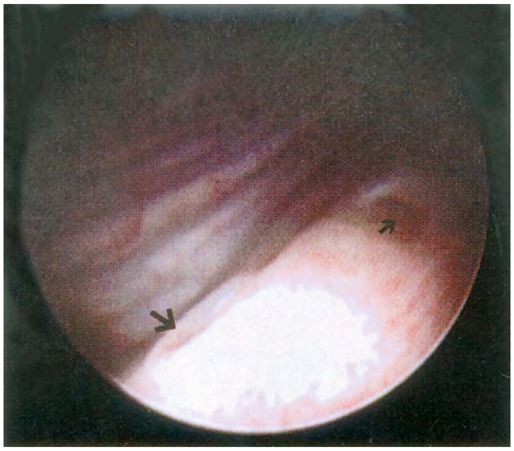

Figure 6-9 Ureteral duplication, with both ureters entering into the bladder. (Upper-pole ureteral orifice, *large arrow;* lower-pole ureteral orifice, *small arrow.*)

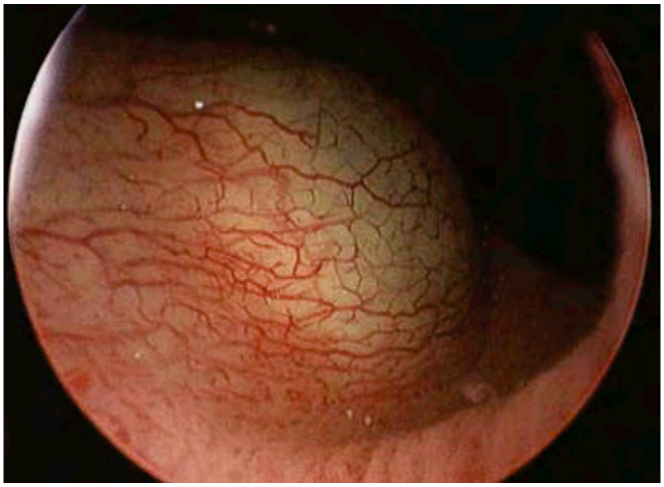

Figure 6-10 Intravesical ureterocele.

Ureteral ectopia may be identified with careful evaluation of the urethra during cystoscopic examination. Once ectopia is identified, placement of stents endoscopically into the ureter is helpful to permit identification during reconstruction (Fig. 6-12). Ectopic ureters that subserve the functioning upper-pole moiety of a duplicated system can be managed with ureteral reimplantation.[22] If the upper pole is minimally functional, then upper-pole partial nephrectomy is the management of choice. Bilateral single-system ureteral ectopia is managed with ureteral reimplantation and possible later bladder neck reconstruction to provide continence.[23]

Tumors

Tumors in children are noted rarely. Most often, cystoscopy is used to identify a lesion that has been noted on radiographic study. The most commonly noted lower urinary tract tumors

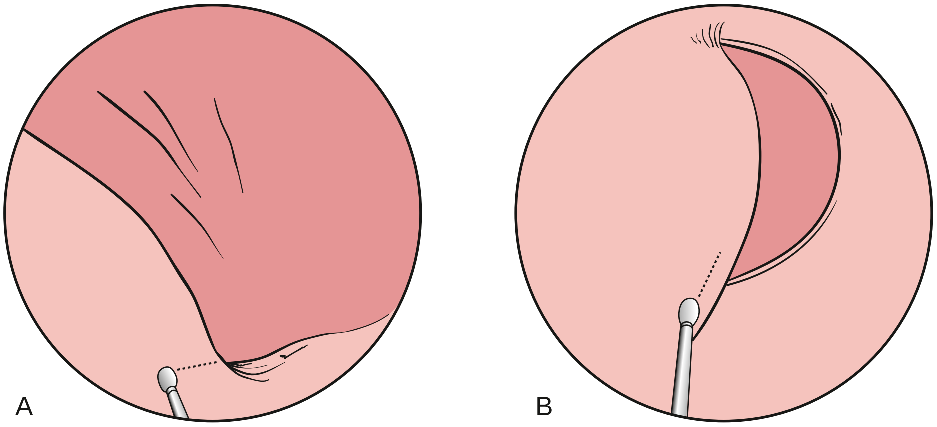

Figure 6-11 **A,** Incision of intravesical ureterocele performed as low as possible in the bladder. **B,** Incision of the ureterocele should be extended distally into the bladder neck component, if present.

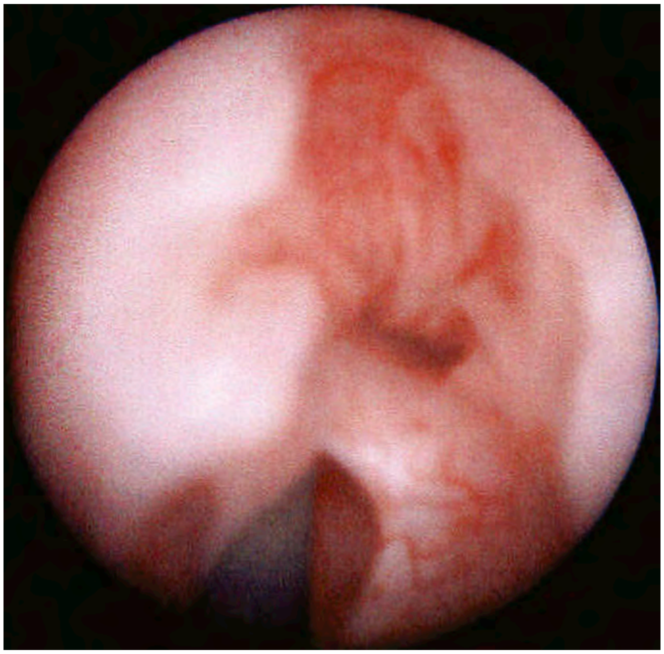

Figure 6-12 Ectopic ureter extending into the urethra cannulated with guidewire.

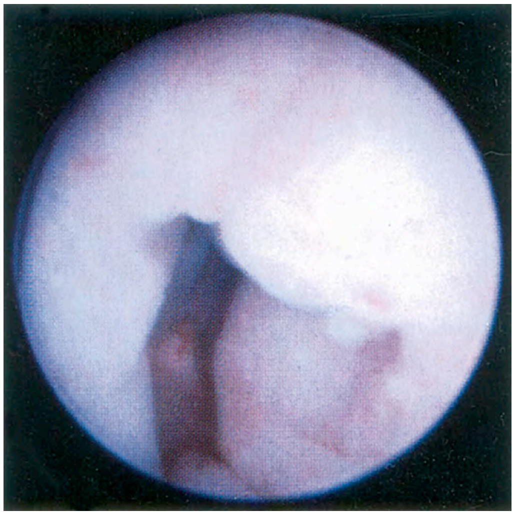

Figure 6-13 Prostatic rhabdomyosarcoma. (Courtesy of Umesh Patil, MD.)

in children are rhabdomyosarcomas of the bladder or prostate (Fig. 6-13). Cystoscopy may be used to determine the preoperative extent of tumor and to obtain biopsies to confirm diagnosis. The increased utility of bladder preservation regimens[24] may leave bladders with residual deformity.[25] Cystoscopy may be needed for follow-up in patients who have undergone bladder-sparing procedures.

Ambiguous Genitalia

Endoscopy is routinely performed to plan reconstruction in children with ambiguous genitalia. Endoscopy of the various perineal orifices may help to determine the relationships among the components of the urogenital tract.[26] The location of the vaginal entry into the urogenital sinus in girls with virilization secondary to congenital adrenal hyperplasia is used to determine the type of procedure required for reconstruction.[27] The vaginal orifice in the urethra in these children may be noted as a small orifice at the tip of the verumontanum (Fig. 6-14). This opening can at times be entered with the smaller cystoscopes and vaginoscopy performed (Fig. 6-15).[28] Catheterization of the vagina with a Fogarty balloon catheter is helpful for identification of the vagina during vaginoplasty (Fig. 6-16).[27]

Strictures

Strictures in children may be congenital,[29] but more commonly are secondary to instrumentation or trauma (Fig. 6-17).[30] Urethral catheterization, fulguration of posterior urethral valves, and hypospadias repair have all been implicated in the development of pediatric strictures (Fig. 6-18).[31] Endoscopic incision using a cold or hot knife or laser ablation can be performed. Endoscopic approaches appear to be efficacious for short strictures, but recurrences are frequent, and open repair is necessary in a large percentage of children.[32]

Vesicoureteral Reflux

The current initial management of vesicoureteral reflux (VUR) includes prophylactic antibiotics and radiographic follow-up. Children who do not have resolution of reflux on follow-up and have breakthrough infections despite adequate correction are candidates for surgical correction.

Earlier studies demonstrated a correlation between the morphology of the ureteral orifice and the length of the submucosal tunnel and potential for resolution. Further study has demonstrated that this correlation is not consistent.[33]

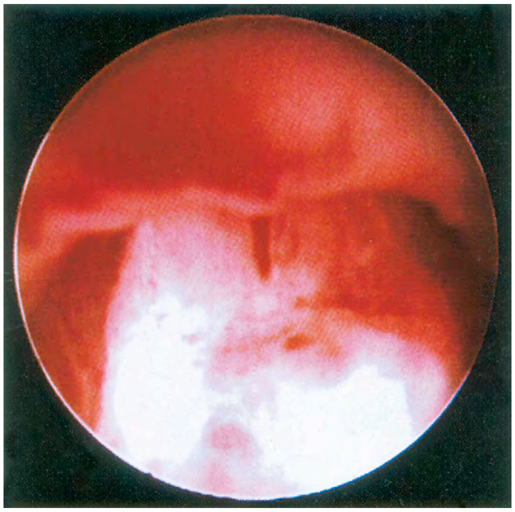

Figure 6-14 Entry of the vagina into the urogenital sinus.

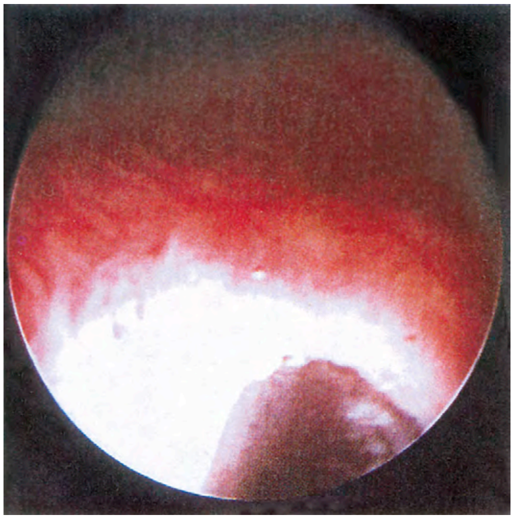

Figure 6-16 A Fogarty catheter inserted into the vaginal orifice for identification during vaginoplasty.

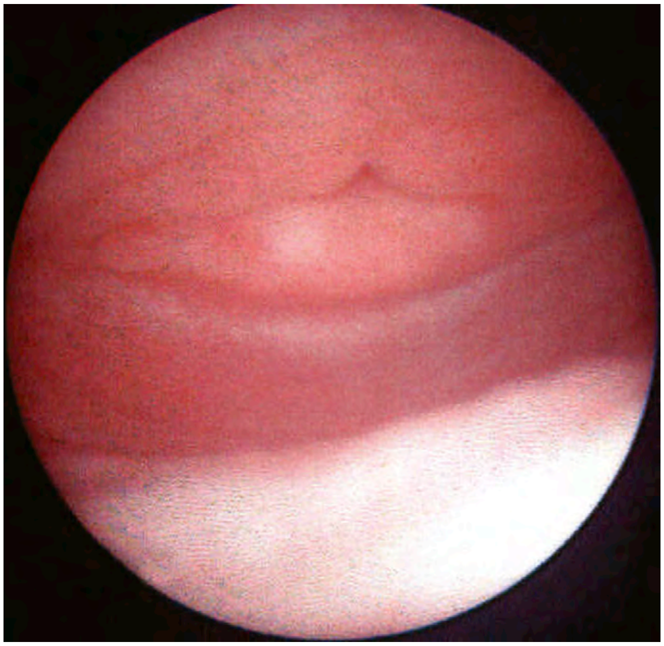

Figure 6-15 Endoscopic evaluation of the vagina and cervix.

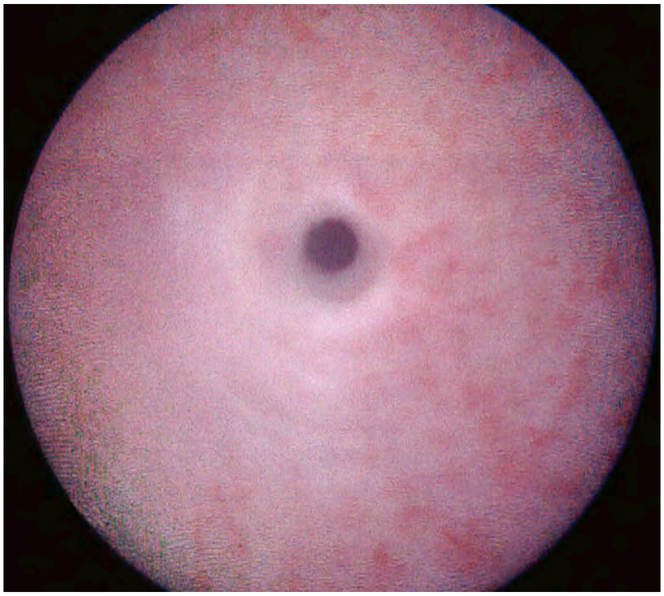

Figure 6-17 Urethral stricture in 7-year-old boy with no prior history of trauma.

Endoscopy has been increasingly used for the treatment of VUR. Teflon has been used for many years for correction of reflux in children.[34] Despite large series of children being treated successfully, questions continue to be raised regarding the long-term potential for migration of Teflon particles to the brain and lungs.[35] This potential has led to the investigation of agents that have greater biocompatibility. Bovine cross-linked collagen has been used for this application, but absorption of collagen may lead to the requirement for repeat procedures for complete correction of reflux.[36] Collagen is therefore no longer used for this application.

The approval of dextranomer hyaluronidase (Dx/HA) for the management of reflux has led to significant improvement in the success rate of endoscopic correction.[37] In many institutions, the high success rate with Dx/HA has led to reevaluation of the primary management of VUR.[38] Injection of Dx/HA is performed in a manner similar to that described for the injection of Teflon (Figs. 6-19 and 6-20).

Some children who present with recurrent urinary tract infections do not have VUR demonstrated by radiographic or radionuclide voiding cystourethrography but have pyelonephritis demonstrated on technetium 99m dimercaptosuccinic acid (Tc^{99m}-DMSA) renal scanning. They may be evaluated with positional instillation cystography to identify occult VUR.[39] If VUR is identified, correction with Dx/HA may be performed simultaneously.

Follow-up after Reconstruction

Endoscopic evaluation may be indicated for follow-up of the urethra and bladder as a precedent to or after complex reconstruction. In children with bladder and cloacal exstrophy,

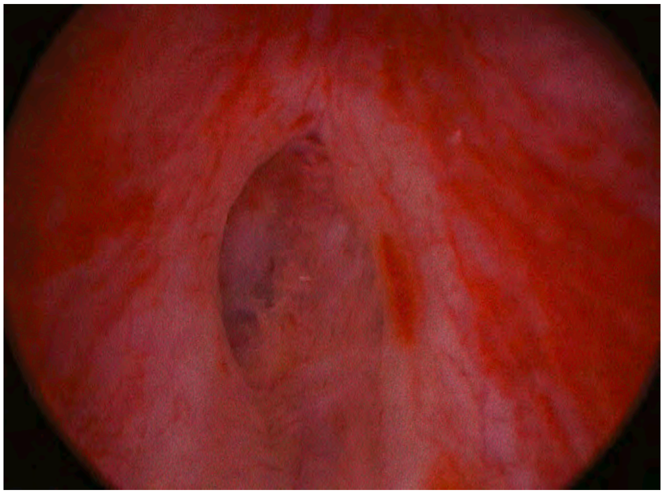

Figure 6-18 Urethral tear secondary to inflation of Foley balloon in the bulbar urethra.

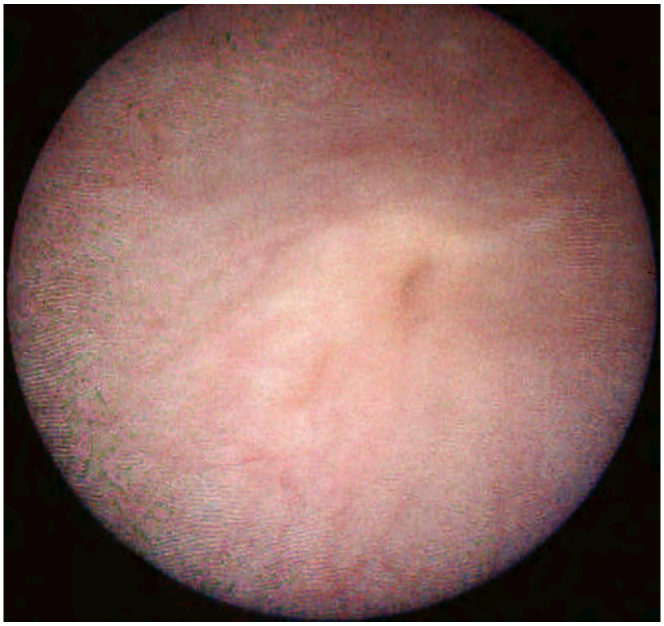

Figure 6-19 Left refluxing ureter before injection of dextranomer hyaluronidase (Dx/HA).

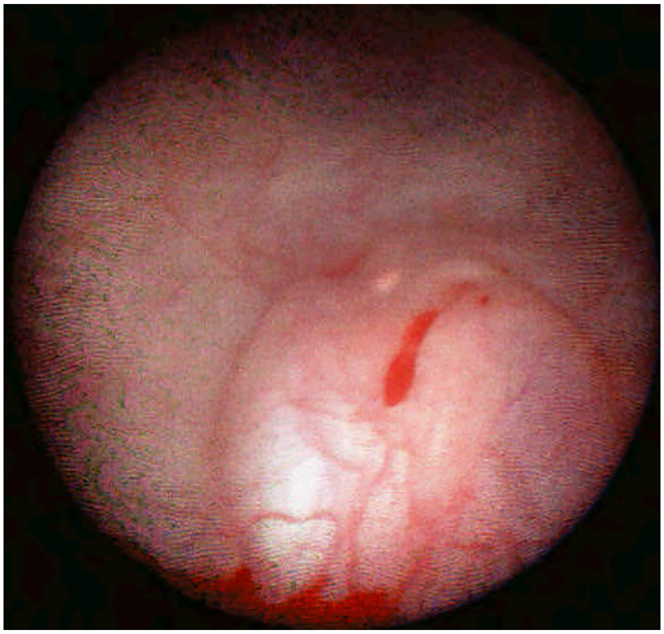

Figure 6-20 Left ureter after successful injection of dextranomer hyaluronidase (Dx/HA).

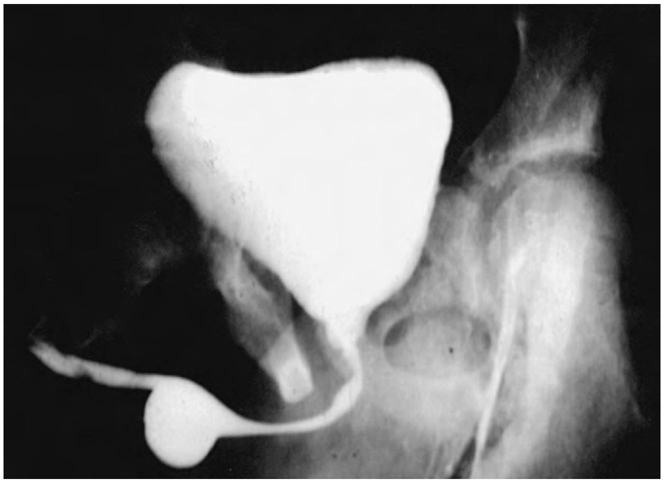

Figure 6-21 Anterior urethral diverticulum identified on voiding cystourethrography. (Courtesy of Umesh Patil, MD.)

assessment of bladder volumes prior to bladder neck reconstruction is essential. Additionally, assessment of the urethra after initial closure to determine adequate patency is critical to permit bladder emptying and prevent upper tract dilatation and deterioration.

Bladder Calculi

Bladder calculi are infrequent in children in developed countries. Most instances of bladder calculi are related to congenital malformation or neurogenic bladder.[40] The increased use of continent pouches made of bowel in children with neurogenic or other abnormalities with diminished bladder capacity have made bladder calculi more frequent in this population.[41] Transurethral stone fragmentation can be performed in children with patent urethras. Endoscopy through the continent catheterizable stoma may be performed, but aggressive attempts at stone removal through the stoma may potentially disrupt the catheterizable channel. Percutaneous access directly into the pouch is easily accomplished and is safe.[41] Fragmentation can be performed with electrohydraulic lithotripsy or with ultrasonic probes using rigid endoscopic instruments.

Fragmentation of stones should be performed against the bladder segment if possible, because perforation of the bowel segment may occur with overzealous attempts at stone fragmentation.

Anterior Urethral Valves

The clinical presentation in infants with anterior urethral valves ranges from mild urethral dilatation to bilateral hydronephrosis and renal dysfunction.[42] The diagnosis is based on finding penile ballooning at voiding cystourethrography (Fig. 6-21).[43]

An anterior urethral diverticulum is an associated finding on cystoscopy.[44] Vesicostomy is the recommended management in infants with high-grade obstruction.[42] However, transurethral ablation has been performed in infants with an adequate-caliber lumen and good associated spongiosal tissue to prevent fistula formation.[43]

Urethral Polyps

Urethral polyps occur occasionally in infants and children presenting with hematuria and voiding disorders. These polyps are usually noted in the posterior urethra of boys[45] but rare cases have been noted in girls.[46] They may be identified as a filling defect on voiding cystourethrography. They are universally benign, and transurethral resection is curative.[45] They may also be ablated transurethrally with the use of laser.[47]

CONCLUSION

Improvements in instrumentation have permitted significant advances in endoscopic evaluation of pediatric urologic problems. Increasingly, endoscopic means are being used for management of many pediatric lower urinary tract problems. As experience increases, these techniques are changing the paradigms for management in pediatric urology. All but the smallest of infants can now be successfully instrumented. Caution needs to be exercised when instrumenting the pediatric urethra, because aggressive efforts to visualize or treat problems can lead to potential injury with lifelong consequences.

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CHAPTER 7

LAPAROSCOPY IN PEDIATRIC UROLOGY

C. K. Yeung and A. A. Thakre

For more than a century, surgeons have depended on external illumination from the operating room light and large incisions for adequate exposure to obtain good surgical vision: hence, the golden motto, "Big Surgeon, Big Incision." The advent of fiberoptics, particularly with the introduction of the rod-lens system in modern endoscopes, changed this rule altogether. Surgeons can now see very clearly with good illumination inside any body cavity without having to make a big incision. This has led to the new era of laparoscopy and minimally invasive surgery (MIS). Pediatric surgeons were quick to grasp this new invention, with Steve Gans first pioneering the use of peritoneoscopy for diagnosis of undescended testes in the early 1970s. Since then, major advances have been made in the application of MIS techniques in various pediatric urologic conditions. Propelled by the fast development of more optically refined and tiny instruments specially geared for use in small infants and young children, there has been a rapid expansion in the spectrum of MIS pediatric urologic procedures, particularly over the past 10 years. Discussions among pediatric surgeons and pediatric urologists about the use of laparoscopy are no longer whether it is feasible in young children but about how best one can apply it successfully in various conditions.

Pediatric urologic operations that can now be regularly performed using the MIS technique comprise many simpler procedures, such as orchidopexy for undescended testes, varicocelectomy, nephrectomy or heminephroureterectomy for nonfunctioning kidneys or dysplastic renal moieties, laparoscopy for diagnosis and gonadectomy for ambiguous genitalia or intersex, and localization and excision of "invisible" dysplastic kidneys with ectopic ureteric insertion causing urinary incontinence, as well as more sophisticated reconstructive procedures, such as laparoscopic dismembered pyeloplasty for hydronephrotic kidneys with ureteropelvic obstruction, pneumovesicoscopic ureteric reimplantation for vesicoureteric reflux (VUR), excision of complicated prostatic utricles, excision of ureteroceles and cecoureteroceles with simultaneous bladder base and bladder neck and posterior urethral reconstruction, endoscopic removal of urinary calculi, laparoscopic bladder neck sling or various reconstructions, augmentation cystoplasty, uretero-ureterostomy, Mitrofanoff appendicovesicostomy, and others. In essence, more than 90% of the operative procedures that were conventionally performed with an open approach and required big open incisions can now be very safely and effectively performed using the MIS technique.

SPECIAL ADVANTAGES OF MINIMALLY INVASIVE SURGERY IN PEDIATRIC UROLOGY

There are several special advantages of using the MIS approach for various pediatric urologic procedures. First, the laparoscope provides a well-illuminated and significantly magnified view of all anatomic structures deep in the pelvis, and even down to the pelvic floor. This view appears to be superior to the view that is obtainable via an open approach. This makes it ideal for operations in the bladder base, bladder neck, and posterior urethra, even in the small pelvic cavity of a young infant, which previously was rather inaccessible by routine open surgery. For instance, a bladder neck reconstruction procedure or excision of a complicated prostatic utricle can now be accomplished using the laparoscope, with a remarkably clear and magnified endoscopic vision that would have been hard to imagine just a few years ago.

Second, the panoramic view of both the abdominal and the pelvic cavities provided by the laparoscope allows exploration and surgery to both the upper and the lower urinary tract at the same setting, avoiding the need for multiple operations or separate, long incisions. Surgical operations for pathologies affecting both the upper and lower urinary tracts, which previously had to be undertaken in multiple stages, can now be easily completed with the use of the laparoscope in one single stage. For instance, traditional management of a duplex kidney with a nonfunctioning moiety that is associated with a dilated megaureter and a complicated prolapsing cecoureterocele necessitated multiple staged operations, usually commencing with an upper-pole heminephroureterectomy via a loin muscle-cutting incision, followed by excision of the cecoureterocele, then reconstruction of the bladder base via a suprapubic Pfannenstiel incision, and finally reimplantation of the lower-moiety orthotopic ureter. These can now all be accomplished in a single setting with the use of the MIS technique.

Third, infants and young children are particularly susceptible to postoperative pain and separation anxiety, and any maneuver that can significantly reduce surgical trauma, minimize postoperative pain, and shorten the hospital stay is a major advantage. The advent of the MIS technique allows pediatric urologists to dramatically change our traditional practice and convert major urologic procedures that used to require prolonged hospitalization to a short-stay or even a one-day surgical procedure. For instance, a traditional open Cohen ureteral reimplantation using a classic suprapubic open incision would normally require a hospital stay of at least 1 to 2 days, the use of urethral urinary diversion, and possible ureteric stenting or extravesical wound drainage. In sharp contrast, a young infant undergoing a similar Cohen reimplantation that is performed with our pneumovesicoscopic technique can now be discharged home on the same evening, with almost no wound pain and without any drains or stents. The much superior wound cosmesis serve as an additional bonus.

SPECIAL TECHNICAL CONSIDERATIONS FOR LAPAROSCOPY IN PEDIATRIC UROLOGY

Although the MIS techniques may result in less surgical trauma, decreased parietal complications, faster recovery, and better wound cosmesis, it must be realized that laparoscopic renal surgery and other MIS urologic procedures in children involve special technical considerations and carry their own morbidity and complications. During laparoscopy, the surgical anatomy and access of the pediatric urinary tract deserve particular attention. For instance, endoscopic renal surgery in children can be performed either from the anterior, through a transperitoneal laparoscopic approach, or posteriorly, through a retroperitoneoscopic approach. Either approach has its advantages and disadvantages, and advocates as well as opponents. We recommend a logical, selective use of the two approaches to suit individual cases according to the position of the diseased renal unit, the absence or presence of a dilated refluxing ureter, and the need for ureterocelectomy and lower urinary tract reconstruction. Likewise, endoscopic bladder and ureteric surgeries in children can be performed by a transperitoneal or an extravesical technique, or with an pneumovesicoscopic, intravesical approach using carbon dioxide bladder insufflation. Each surgical approach involves different equipment, operative room setup, and technical considerations. Pediatric urologists should familiarize themselves with the various techniques before embarking on more sophisticated laparoscopic procedures.

SURGICAL ANATOMY AND ACCESS IN LAPAROSCOPIC RENAL SURGERY: TRANSPERITONEAL VERSUS RETROPERITONEAL APPROACH

One of the common debates in pediatric laparoscopic renal surgery is the choice for a most suitable way to access the kidney and the urinary tract. The transperitoneal route has been a preferred route for most pediatric urologists because of the familiar anatomy and wider operating space.[1-3] This approach is also useful to reach the lower urinary tract, the testis, and the spermatic vessels. A retroperitoneoscopic approach in pediatric urology has been well established since its success in adult urology after Gaur's discovery of the use of a balloon to create the retroperitoneal space.[4-8] With a transperitoneal approach, access to the anterior aspect of the kidney within Gerota's fascia can be readily obtained when the overlying colon is detached from its lateral peritoneal attachment and reflected medially. Subsequent endoscopic renal surgery can then proceed rather intuitively, because the kidney together with its vascular pedicle and the surrounding organ structures are clearly visible and are orientated in the usual manner. In contrast, a much better understanding and familiarity with the surgical anatomy of the retroperitoneum is required for effective and complication-free retroperitoneoscopic surgery. The identifiable organ structures and anatomic landmarks in the retroperitoneal space are much fewer than in the peritoneal cavity, and they are often obscured by fibrofatty tissue during the initial phase of gaining surgical access. The only consistent boundary of the retroperitoneal space is at its posterior border, formed by attachment with the paraspinal muscles and the origin of the main branches from the great vessels. The anterior and lateral boundaries are formed by the detachable and relatively mobile peritoneal reflection, which can be considerably displaced forward and medially by a combination of balloon dilatation and blunt instrument dissection. Before proceeding to further dissection, one must clearly identify the available anatomic landmarks and obtain an accurate surgical orientation. Failure to do so leads to unnecessary surgical maneuvers, prolongs the operation time, and often causes undesirable complications.

During retroperitoneoscopic surgery, the posterior aspect of the kidney is approached. Compared with a transperitoneal view, the kidney, as visualized under retroperitoneoscopy, usually lies in a more vertical or caudad-to-cephalad orientation (Fig. 7-1). The lower pole of the kidney, lying on the psoas muscle, is encountered first, and these two structures serve as the most reliable and important anatomic landmarks. Endoscopic dissection can then proceed further along the posterior surface of the kidney to identify the renal hilum and the upper pole. In a child without excessive retroperitoneal fat, the ureter leading to the renal hilum and the pulsatile renal artery, together with its accompanying renal vein, can usually be visualized early in the dissection. Other reliable anatomic landmarks include the aorta pulsation on the left side and the inferior vena cava and duodenum on the right side. In cases in which the initial balloon dissection of the retroperitoneal space falls outside Gerota's fascia, the silvery reflection of the peritoneal lining itself and the intraperitoneal organs, especially the spleen on the left and the liver on the right, can be seen moving with respiration through the semitransparent peritoneum. These can also serve as guides for surgical orientation and the limits for retroperitoneal dissection.

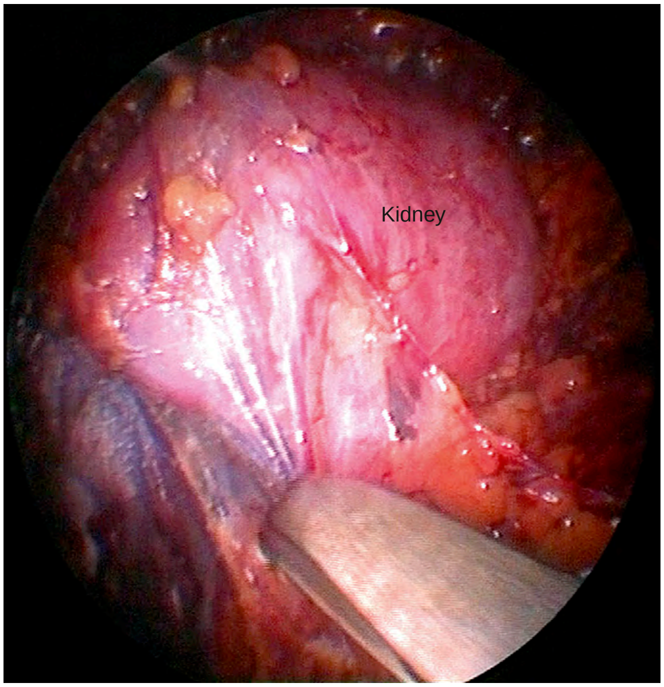


Figure 7-1 Port site for left retroperitoneal nephrectomy.

Because the urinary tract is located in the retroperitoneal space, it would appear more logical to directly approach the kidney and renal hilum posteriorly, via a retroperitoneal route, thereby avoiding the potential risks and complications that may be associated with transgression and surgical manipulation in the peritoneal cavity.

Retroperitoneoscopic renal surgery can be done with the patient in either a prone or a lateral position. Operative space is created with either balloon dissection or a simple dissection using the tip of the laparoscope with the help of gas insufflation (pneumodissection) (Fig. 7-2).[7,8] Retroperitoneoscopic renal surgery typically follows all the steps of open renal surgery. It has the potential advantages of (1) reduced risk of injury to intraperitoneal organs; (2) more direct access to the kidney, renal pelvis, and renal vascular pedicles; (3) reduced risks of contamination of the peritoneum from any renal pathology (urinary leak, infection, or neoplasm); and (4) fewer exposure problems from liver, spleen, or bowel obscuring the operative field. In contrast, the transperitoneal approach provides greater working space and more easy access to the distal ureter, bladder and bladder base, and proximal urethra. Selective use of either technique is recommended to suit individual cases.

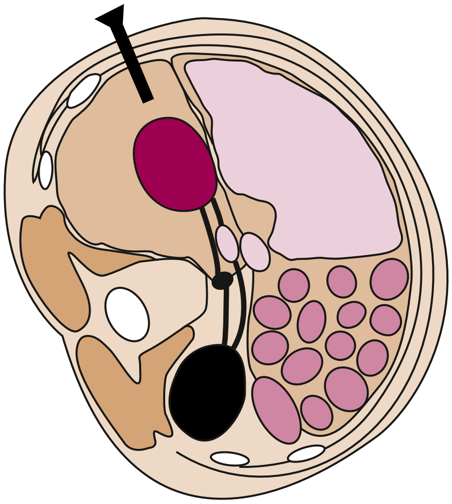


Figure 7-2 Retroperitoneal space access for right nephrectomy.

The position of the kidney, the presence or absence of a dilated refluxing ureter, and the need for ureterocelectomy are the major determining factors. Simple nephrectomy for a kidney that is nonfunctioning due to multicystic renal dysplasia or ureteropelvic junction (UPJ) obstruction, or partial nephrectomy for upper-moiety duplex with a nonrefluxing ureter, can be performed via a posterior retroperitoneoscopic approach. Nephrectomy for VUR or nonfunctioning kidney in older children (>5 years) and partial nephrectomy for duplex systems requiring excision of grossly dilated megaureters can be done with a more lateral extraperitoneal approach to gain access to the lower end of the dilated ureter. For small, ectopic, "invisible" kidneys or complex duplex excision with extensive ureterocelectomy and lower urinary tract reconstruction, a transperitoneal approach is recommended.

NEPHRECTOMY

Nephrectomy is perhaps the most popular urologic indication for the laparoendoscopic procedure.[9] The first reported case was managed with a transperitoneal approach, but a large number of series now report successful retroperitoneoscopic nephrectomy.[10-13] In children, the indications comprise exclusively benign diseases such as multicystic or dysplastic kidneys causing renal hypertension, nonfunctioning kidneys associated with reflux nephropathy, obstructive uropathy, xanthogranulomatous pyelonephritis, calculus disease, and protein-losing nephropathy (pretransplantation nephrectomy).[14] The contraindications for laparoscopic nephrectomy are relative and include previous intra-abdominal or retroperitoneal surgery, renal trauma, severe cardiopulmonary disease, severe coagulopathy, and malignant renal tumors. Recently, there have been reports on the feasibility of laparoscopic nephrectomy for unilateral Wilms' tumor after chemotherapy.[15]

The surgical technique of laparoendoscopic nephrectomy is similar regardless of the approach used. In transperitoneal nephrectomy, the colon is first reflected from the kidney by incision of the lateral line of Toldt. In most cases, the ureter can be identified and used as a handle to lift the lower pole of the kidney. This maneuver facilitates access to the hilar vessels and their dissection. We use a 5-mm clip applicator for the surgical clips (titanium and Hemolok) without any problem. Some authors suggest using absorbable ties, bipolar cautery, harmonic scalpel or LigaSure for smaller arteries; we find the security of clips attractive and feel that they can be efficiently placed. During the hilar dissection, renal arterial branches can be mistaken as the main renal artery due to the enlarged endoscopic view of the vessels. It is therefore a safe practice to search for other branches still needing ligation before the kidney is removed. This is particularly true with dysplastic kidneys, where aberrant arterial supply is common. Dissection of the perinephric tissues may be performed with a combination of rapid blunt and cautery-assisted dissection. In a cystic kidney, it is best to leave the cysts full until most of the dissection is complete, to facilitate blunt dissection. Near completion, it may be helpful to drain some of the cysts, to permit grasping of the cyst walls for application of traction on the kidney to facilitate removal. In most cases, the specimen is put in a small bag, and removal is possible through the umbilical port site, or the initial port site used to create the retroperitoneal access. Larger kidney specimens may require a bigger bag with manual morcellation and extraction.

Instrumentation used for nephrectomy is the same for either approach and usually includes 20-cm long, 5- and 3-mm delicate scissors, dissecting and grasping tools, and a heavy locking grasping device for specimen removal. The radially expanding cannula system (Step, InnerDyne, Salt Lake City, UT) permits moving between 3.5- and 5-mm instruments. These ports are quite secure during the operation and do not fall out easily during the procedure. We also fix the ports externally and have not experienced any significant complications with this system, but the valve mechanisms are fragile and may be damaged with multiple instrument changes.

NEPHROURETERECTOMY

Das and associates[16] reported the first laparoscopic nephroureterectomy in a child. Commonly, this procedure has been done through a transperitoneal route regardless of the child's age, underlying disease, or kidney size.[17] This approach has also been found useful in dealing with an atrophic ectopic pelvic kidney with an ectopic ureteral insertion into the vagina.[18] We have used the transperitoneal approach, but in our experience the lateral retroperitoneal approach has provided better access for a complete ureterectomy.[19] We find the retroperitoneal approach very useful in children who have been undergoing peritoneal dialysis and when extensive peritoneal adhesions are anticipated from prior abdominal surgery. The entire specimen of kidney and the ureter is removed intact, although the extent to which the ureter is removed usually depends on the pathology. In the setting of reflux, the entire ureter must come out. During complete removal of the ureter, care is taken to pass the ureter under the gonadal vessels and to safeguard the vas in boys. The ureter is traced to its insertion into the bladder, where it is closed with intracorporeal suturing, for a large ureter, or by passing a snare ligature for the routine cases. Kobashi and coworkers[20] relied on cystoscopy and fulguration of the intramural ureter and ureteral stump when reflux nephropathy was present and reported success in four of five patients.

PARTIAL NEPHROURETERECTOMY

In children, partial nephroureterectomy is usually performed for a nonfunctioning renal segment of a duplex system associated with ectopic ureteroceles, VUR, or obstruction. A potential advantage with a laparoscopic approach is that wide mobilization of the whole kidney is not necessary in most cases, and therefore the risk of jeopardy to the remnant pole is limited.[21-23] We handle the partial nephroureterectomy in such cases through a different approach. We perform a single-stage laparoscopic heminephroureterectomy of the nonfunctioning moiety in a duplex kidney along with a ureterocele excision and ureteric reimplantation of the refluxing ureter.[24] This approach addresses both ends of the poorly functioning moiety effectively. The patient is placed in a semilateral position. The colon is mobilized medially in its full length to provide an excellent view of the renal pedicle, kidney, pelvis, ureter, and the posterior wall of urinary bladder. The advantage of laparoscopy is clearly highlighted here, because one can easily access the kidney, ureter, and the bladder in the same procedure by just changing the direction of the laparoscope and the working instruments from the upper abdomen to the pelvis. The demarcation between the double-moiety segments is usually very clear; the affected unit is often hydronephrotic or cystic with little blood flow, and this facilitates separation of the two poles.

The critical feature in pediatric partial nephroureterectomy is the delicacy of the renal vasculature of the remnant segment, which is best protected by limiting the mobilization of the remnant pole and by isolating the vessels. Sometimes it is difficult to identify and separate the upper-pole vessels; in that case, the parenchymal transection is started before vascular control of vessels supplying the upper pole is obtained. The parenchyma can be transected by electrocautery, but we prefer the harmonic scalpel with curved jaws, because it provides a precise and accurate cut at the junction between the upper and lower poles.[25,26] The lower-pole partial nephrectomy is technically more demanding than an upper-pole nephrectomy, because identification of the lower polar vessels requires a full dissection of the pedicle, and the line of demarcation is less evident than what is seen for an upper-pole nephrectomy.

LAPAROSCOPIC ADRENALECTOMY

Laparoscopic adrenalectomy is not a very commonly performed operation in children. It has been performed in children for the traditional indications, although it is contraindicated in patients with malignant adrenal lesions.[27,28] The approach is either transperitoneal or retroperitoneal. Both approaches have been used successfully and have demonstrated comparable blood loss and hospital course.[29,30] The transperitoneal approach has been used more commonly for the resection of pheochromocytoma and bilateral adrenal tumors (congenital adrenal hyperplasia) refractory to medical treatment. A retroperitoneal approach may be useful if the patient has previously undergone an abdominal operation. In a recent review of literature, a total 109 cases were reported; the transperitoneal approach was undoubtly preferred for right adrenalectomy (95.2% of cases), whereas left adrenalectomy was performed by retroperitoneoscopy in 30% of reported cases.[31]

LAPAROSCOPIC PYELOPLASTY

Open Anderson-Hynes pyeloplasty has been widely accepted as the surgical treatment of choice for UPJ obstruction in children, with a success rate of more than 90% in most reports.[32-35] Laparoscopic pyeloplasty in children and infants is a technical challenge, although it is feasible and has been reported with adequate early results.[36-38] Peters and colleagues[39] described the first successful case in a child in 1995. A three-port transperitoneal access technique is popular, and good results have been reported (Fig. 7-3). On the left side, a transmesenteric approach is useful. A small opening is made in the mesentery to expose the UPJ. This avoids mobilizing the left colon, thus decreasing the amount of time and tissue disruption required for exposure. On the right side, the colon is mobilized, although the UPJ is often easily exposed behind the broad peritoneal reflection, lateral and superior to the hepatic flexure.

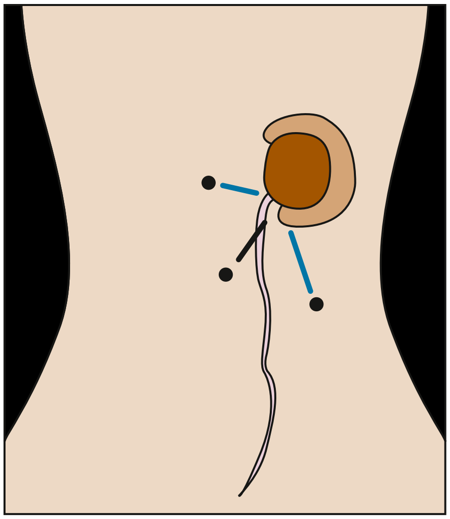


Figure 7-3 Three-port transperitoneal access for performing transmesenteric right pyeloplasty.

Dissection of the UPJ is similar to the technique used in an open approach. If there are no crossing vessels, the dissection is straightforward. Once the UPJ has been isolated, it is ligated and divided, leaving a tag of suture on the ureter. This provides a handle for manipulation during the procedure, with minimal trauma to the remaining ureter. It is helpful to place a holding stitch on the renal pelvis and pass it through the anterior abdominal wall to steady the anastomosis (Fig. 7-4). If crossing vessels are identified, the ureter is dissected posteriorly until the UPJ is seen behind the vessels. The ureter can be divided just below the UPJ. At that point, attention is turned to the anterior pelvis. As this is freed, the UPJ can be brought anterior to the vessels, where the anastomosis can be performed. The vessels themselves require no manipulation. The ureter is spatulated laterally with a 3-mm scissor. which objectively widens the anastomosis (Fig. 7-5) and makes placement of the most caudal sutures technically more straightforward.

The anastomosis is started with interrupted sutures at the dependent part of the renal pelvis (Fig. 7-6). Fine absorbable suture is used (6-0 polyglactic acid suture). A small curved needle, such as a taper, is preferred. This can pass through a 3- or 5-mm port. When passing the needle, it is important not to blunt the tip. One of the biggest challenges in laparoscopic pyeloplasty is the technical difficulty of suturing a small-caliber ureter. This can be even more challenging when trying to sew around an internal stent. A stent is placed retrograde over the previously positioned guidewire after the posterior anastomosis is completed (Fig. 7-7). The rest of the anastomosis can be done with either an interrupted or a running suture (Fig. 7-8). A double pigtail stent is left in place for 2 to 4 weeks. We leave an indwelling Foley catheter for 24 to 48 hours. In most cases, an external drain is not necessary.

Surgical Technique: Retroperitoneal Pyeloplasty

Our preferred technique is by the retroperitoneal approach.[36] After inducing general anesthesia, a urethral catheter is inserted, and the bladder is filled with methylene blue

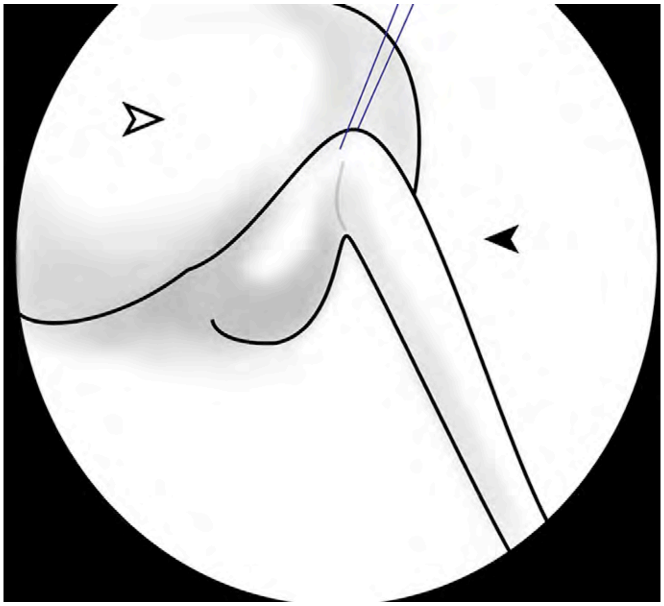


Figure 7-4 Holding stitch on the pelvis passed through the anterior abdominal wall.

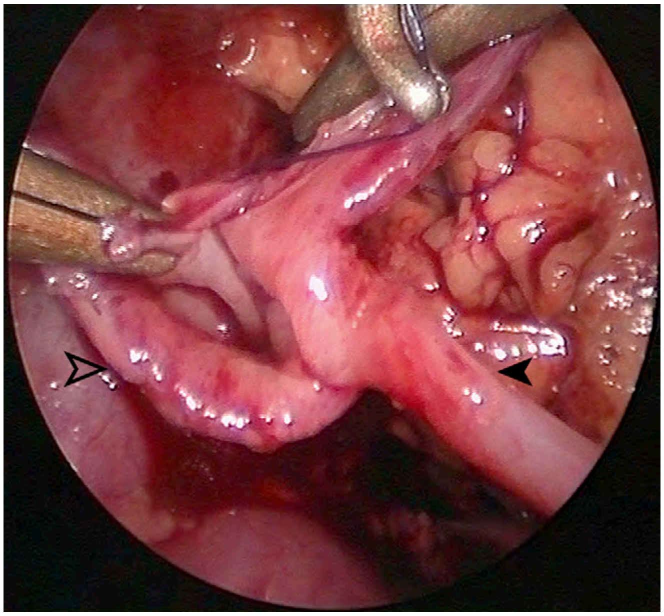


Figure 7-6 Wide funneling of the new reconstructed ureteropelvic junction. *Arrows* show the cut pelvis and the ureter.

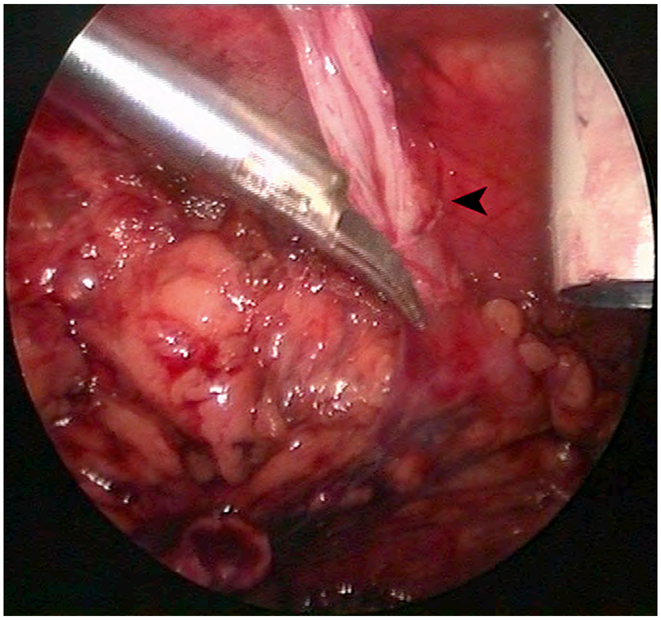


Figure 7-5 Lateral spatulation of the ureter.

solution. We do not do a preliminary cystoscopy and ureteric stenting. The patient is placed in a semiprone position. A 1- to 2-cm incision is made over the midaxillary line, about 4 cm above the iliac crest. The retroperitoneal space is created with a glove balloon. We use three Step ports (5 mm) and use 5-, 3.5-, and 3-mm instruments depending on the intraoperative need. A fourth port is placed for retraction. Video retroperitoneoscopy is performed using a 5-mm, 30-degree laparoscope. Gerota's fascia is opened to expose the lower pole of the kidney, the dilated renal pelvis, and the upper ureter. The UPJ is identified, and the line of pelvic reduction is planned. A 4-0 polydioxanone suture over a straight needle is passed percutaneously through the abdominal wall to the upper pole of the renal pelvis and then back through the abdominal wall again at the same point. This serves as a "hitch stitch" to stabilize and present the pelvis and to mark the upper limit of the line of pyeloplasty during subsequent pelviureteric anastomosis. It should not be placed too far from the line of pelvic transection and anastomosis; hence, in a patient requiring no extensive pelvic reduction, it is placed low on the pelvis.

The UPJ is dismembered, the pelvis trimmed, and the upper ureter spatulated. A short (2 to 3 cm) segment of 5F (1.65-mm) feeding tube is then inserted into the open end of the spatulated proximal ureter to separate its anterior and posterior walls. This allows accurate placement of the first corner suture over the apex of the spatulated upper ureter and the most dependent part of the reduced renal pelvis. Pelviureteric anastomosis is carried out using continuous Biosyn 7/0 for infants and Biosyn 6/0 for younger and older children.

After the posterior layer of the anastomosis is completed, a transanastomotic, double-pigtail stent is inserted by first passing an 18-gauge venous cannula through the abdominal wall. A flexible guidewire is then inserted through the cannula, manipulated into the upper ureter, and advanced into the bladder. The cannula is then withdrawn, and a 4F (1.32-mm) or 5F double-pigtail catheter is passed over the guidewire into the bladder, with the proximal end of the pigtail positioned in the renal pelvis. The entry of the catheter into the bladder can be sensed by seeing efflux of blue-colored fluid that has previously filled the urinary bladder. The anterior layer of the pelviureteric anastomosis is then completed with continuous fine sutures of Biosyn and tied intracorporeally at the upper corner with the suture from the posterior layer of anastomosis. The hitch stitch is removed, and the UPJ and upper ureter are inspected to ensure that no kinking occurs.

In our technique,[36] we have applied certain technical refinements. The camera port is moved laterally and positioned in the midaxillary line to maximize the available retroperitoneal space. By stripping the peritoneum medially and superiorly under videoscopic vision, the working ports can be sited further apart, to minimize the overcrowding of instruments. Correct positioning of the patient (as described) facilitates the subsequent pelviureteric anastomosis. The insertion of a short

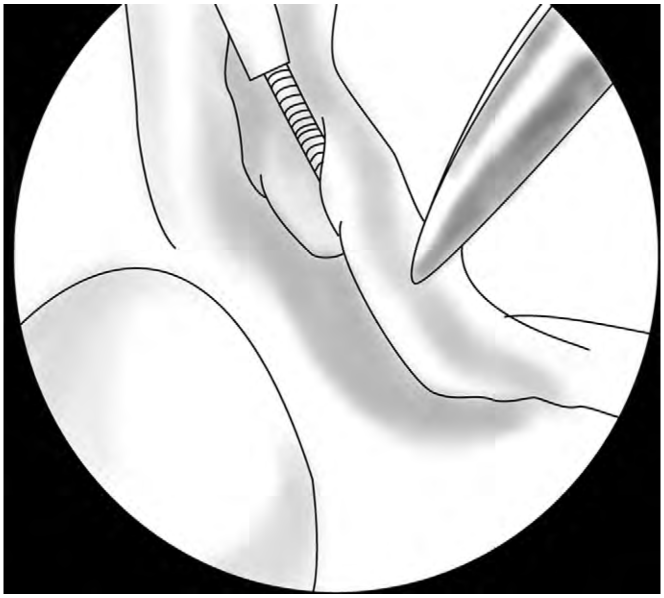


Figure 7-7 Retrograde placement of "JJ " stent over a guidewire.

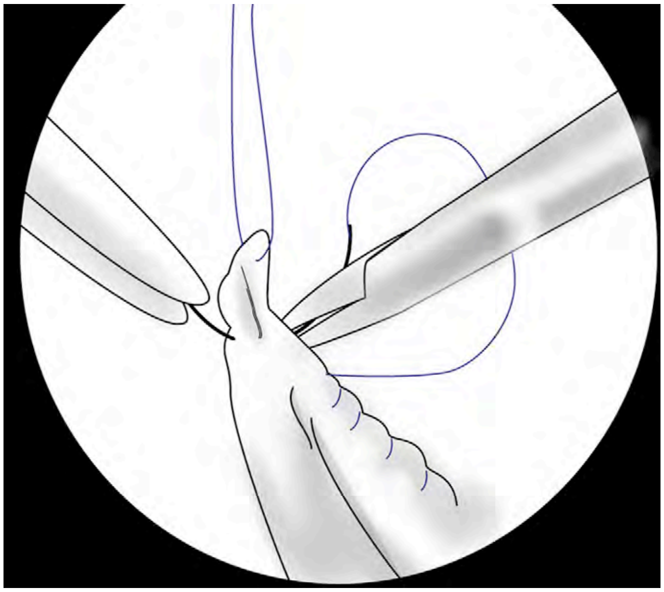


Figure 7-8 Completed pyeloplasty using running suture.

segment of a small feeding tube into the open end of the proximal ureter greatly facilitates the accurate placement of the first corner suture. The availability of 3-mm laparoscopic instruments, particularly the needle holder, allows gentler handling of fine 6-0 sutures, minimizing breakage. Laparoscopic pyeloplasty can be performed in small babies less than 3 months old. Our mean operating time is approximately 120 minutes. Postoperatively, most patients are observed for 24 to 48 hours. Antibiotic prophylaxis is used until the stent is removed. A renal ultrasound study is obtained 6 weeks after stent removal to confirm decreasing hydronephrosis, and a diuretic scan is done at 3 months.

Success of laparoscopic pyeloplasty in adults has been greater than 95%, which is comparable to results with an open approach.[40] Reports in children have shown quicker return to normal activities than after an open procedure, and comparable success.[41] Pediatric laparoscopic pyeloplasty series are still few and small. Further results will serve to document the outcome of this approach.

LAPAROSCOPIC SURGERY FOR VESICOURETERAL REFLUX

Laparoscopic surgical options for correction of VUR are in their initial stage of application in the pediatric population. Both extravesical and intravesical approaches have been demonstrated, and early success rates have matched those of open reimplantation (>95%), with low morbidity through a minimally invasive approach.[42,43] Laparoscopic techniques were initially developed using pigs[44-49] and have now been successfully used in humans.[50-54]

Initial attempts at laparoscopic ureteral reimplantation used an extravesical approach followed by the intravesical approach. The technique of meticulous dissection and suturing remains the mainstay of success in this kind of reconstruction in children The MIS technique has an advantage of excellent visualization and use of small access ports; good early results favor continued development of this approach to reconstruction. We also believe the limitation of small space has been overcome significantly by introduction of the use of small 3-mm instruments.

Surgical Technique: Extravesical Approach

The extravesical approach can be performed unilaterally or bilaterally, applying the Lich-Gregoir technique. The patient is placed in supine position for an extravesical laparoscopic ureteral reimplantation. The bladder is first inspected with cystoscopy. A 3F (0.99-mm) ureteral catheter may be placed at this time to aid laparoscopic identification, although we do not use it. After cystoscopy, the bladder is drained by a catheter. An infra-umbilical incision is made to place a 5-mm trocar for vision by an open method. The other two trocars are placed along the lateral border of rectus. Ports are fixed to the abdominal wall using a stitch which is also used to close the fascia. The ureter is normally seen well at the pelvic brim and can be followed to its insertion into the bladder.

The technique follows the same steps as the open Lich-Gregoir procedure. It starts with dissection of the ureter after the peritoneum is opened just over the posterior bladder wall. In females, the ureter can be found in its anterior relation to the uterus. The ureter is freed from the surrounding tissue, keeping its vessels intact. Approximately 4 to 5 cm is dissected to permit mobility and to prevent kinking as the bladder tunnel is created for the ureter. It is important to take care not to damage the vas during the dissection around the UVJ. A hitch stitch through the posterior bladder wall can be used to improve the exposure of the ureteral hiatus, attaching to the abdominal wall or through it.

Once the ureter is free, the size of the tunnel is estimated after the bladder has been partially distended. The ureter should course slightly laterally to avoid kinking. A tunnel is adequately dissected to obtain a 5:1 ratio of length to width; the detrusor muscle is divided full-thickness with a cautery hook, while the mucosa is kept intact. Any perforations of the mucosa are closed with a 6-0 chromic suture. The ureter is positioned in the tunnel, avoiding any kinking or excessive compression of the ureter to prevent obstruction. Closure may be done from the proximal end of the incision to the distal end

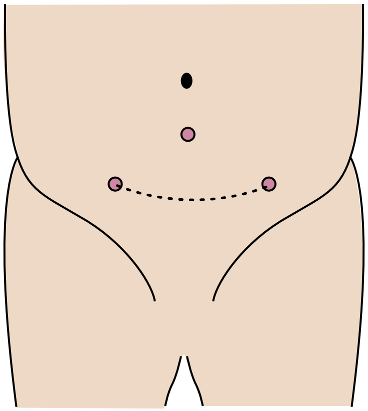


Figure 7-9 The 5-mm working ports are inserted along the interspinous skin crease on either side of the lower lateral wall of the distended bladder under vesicoscopic guidance.

or in the reverse fashion. In the latter case, the ureter is well visualized; in the former, the needle needs to be passed under the ureter each time. The peritoneum is closed in a running fashion, and a catheter is left in place for 1 day.

The indications for using the MIS extravesical Lich-Gregor approach are the same as for the open surgical technique, although some investigators do not find the extravesical procedure appropriate for patients with megaureters requiring tapering.[51]

Surgical Technique: Intravesical Approach

The laparoscopic Cohen procedure using a pneumovesical approach was first described in a pig model, in 2003.[49] The steps of the surgery are the same as for the open approach. The patient is positioned supine with the legs apart for cystoscopy and bladder catheterization intraoperatively. For small infants, the surgeon can stand and operate over the patient's head; for older children, the surgeon usually stands on the patient's left side. The video column is placed between the patient's legs at the end of the table. The port placement is preceded by transurethral cystoscopy to allow placement of the first camera port under cystoscopic guidance.

The bladder is first distended with saline, and a 2-0 monofilament traction suture is passed percutaneously at the bladder dome under cystoscopic vision, through both the abdominal and bladder walls. This helps to keep the bladder wall from falling away when the first camera port site incision is made and during insertion of the cannula. A 5-mm Step port is inserted under cystoscopic vision. A urethral catheter is then inserted to drain the bladder and start carbon dioxide insufflation to 10 to 12 mm Hg pressure. The urethral catheter is used to occlude the internal urethral meatus to secure the CO_2 pneumovesicum, and it could also serve as an additional suction irrigation device during subsequent dissection and ureteric reimplantation. A 5-mm, 30-degree scope is used to provide intravesical vision. Two more 3- to 5-mm working ports are then inserted along the interspinous skin crease on either side of the lower lateral walls of the distended bladder under vesicoscopic guidance (Fig. 7-9). A 3- to 4-cm long segment of a 4F (1.32-mm) or 6F (1.98-mm) catheter is then inserted into the respective ureter as a stent to facilitate subsequent ureteral mobilization and dissection. The stent is secured with a 4-0 monofilament suture (Fig. 7-10). Intravesical mobilization of the ureter, dissection of submucosal tunnel, and a Cohen ureteral reimplantation are then performed under endoscopic guidance, in a similar manner to the open procedure.

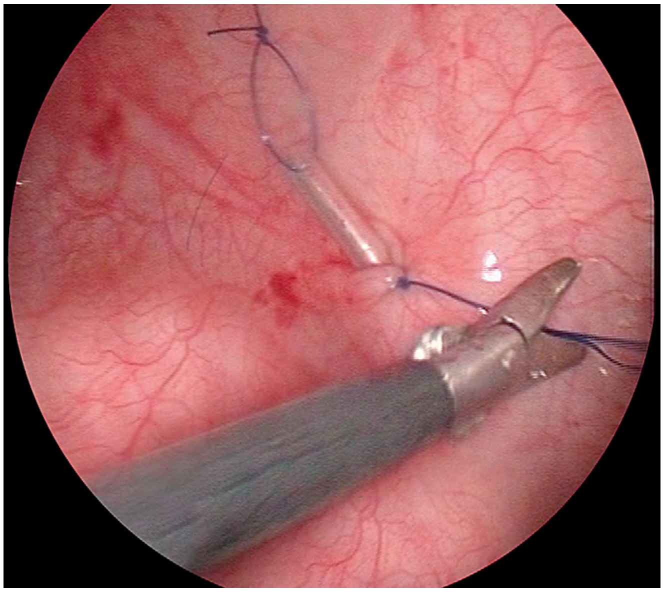


Figure 7-10 A 3- to 4-cm long segment of a 4F (1.32-mm) or 6F (1.98-mm) catheter is inserted into the ureter as a stent to facilitate subsequent ureteral mobilization and dissection and is secured with a 4-0 monofilament suture.

The ureter is mobilized by first circumscribing the ureteral orifice, using hook electrocautery (Fig. 7-11). With traction on the ureteric stent obtained by the use of a blunt grasper, the fibrovascular tissue surrounding the lower ureter can be seen and divided, using fine 3-mm endoscopic scissors and a diathermy hook, while preserving the main ureteric blood supply (Fig. 7-12). Mobilization of the ureter is continued for 2.5 to 3 cm into the extravesical space. Once adequate ureteral length is obtained, the muscular defect in the ureteral hiatus is repaired using 5-0 absorbable sutures, usually with an extracorporeal knot-tying technique (Fig. 7-13). A submucosal tunnel is then created, as in an open Cohen procedure. With the use of a diathermy hook, a small incision is made over the future site of the new ureteral orifice, usually chosen to be just above the contralateral ureteral orifice. Dissection of the submucosal tunnel is then started from the medial aspect of the ipsilateral ureteral hiatus toward the new ureteral orifice, using a combination of endoscopic scissor dissection and the diathermy hook for hemostasis. Once the submucosal tunnel dissection is completed, a fine grasper is passed, and the mobilized ureter is gently drawn through the tunnel.

The anastomosis is performed under endoscopic guidance with intracorporeal suturing using interrupted 5-0 or 6-0 poliglecaprone or polydioxanone sutures (Figs. 7-14, 7-15). A ureteral stent is not routinely used, except for selected patients undergoing bilateral ureteral reimplantation and those with megaureters requiring tapering ureteroplasty. The working ports are removed under endoscopic vision with evacuation of the pneumovesicum. The bladder-holding stitches are then tied. Each port site entry wound is then closed with a subcuticular monocryl suture. The bladder catheter is kept in place for 1 day, and the patient is discharged home and advised to refrain from play for a few days.

Our long-term results of this technique are encouraging, and endoscopic intravesical ureteric mobilization and cross-trigonal ureteral reimplantation can be safely and effectively performed with routine pediatric laparoscopic surgical techniques and instruments under carbon dioxide insufflation of the bladder. This technique has been effective in achieving a high success

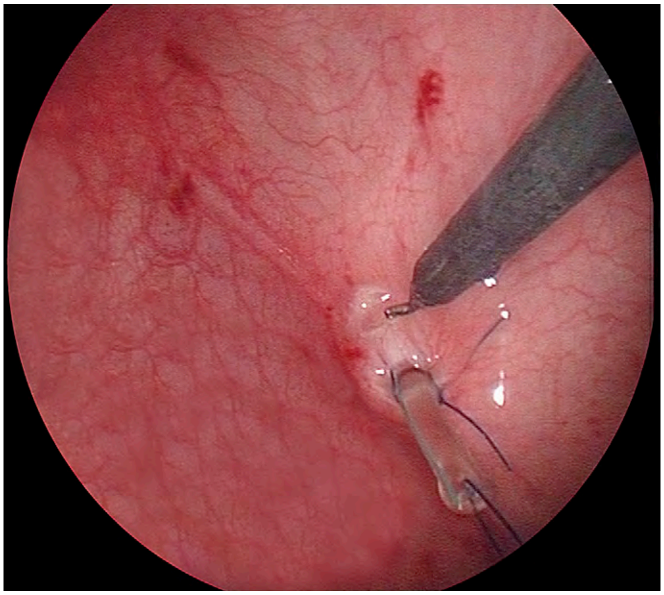


Figure 7-11 The ureter is mobilized by first circumscribing it around the ureteral orifice using hook electrocautery.

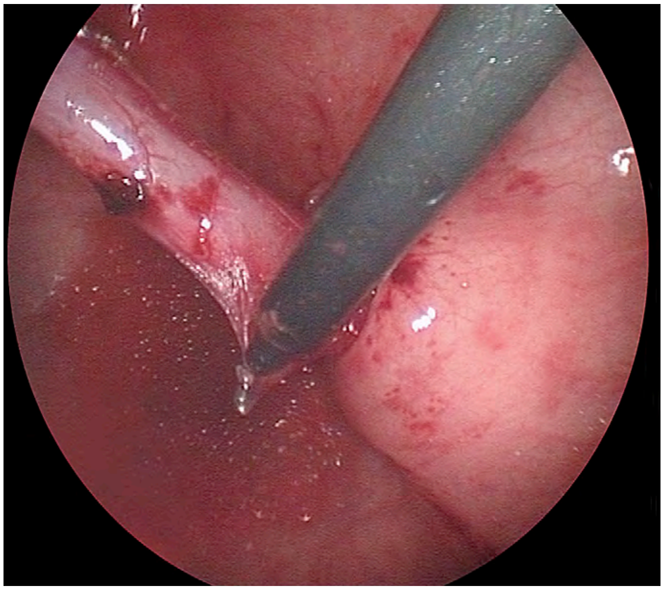


Figure 7-12 With traction on the ureteric stent obtained by the use of a blunt grasper, the fibrovascular tissue surrounding the lower ureter can be seen and divided using fine 3-mm endoscopic scissors and diathermy hook, while preserving the main ureteric blood supply.

rate in reflux resolution, equivalent to the open technique, but with minimal invasiveness and much faster recovery.[54]

OTHER URETERAL SURGERIES WITH CARBON DIOXIDE GAS INSUFFLATION OF THE URINARY BLADDER

Ureterocele excision with a Cohen cross-trigonal ureteral reimplantation and bladder neck reconstruction can be safely performed under carbon dioxide insufflation of the bladder. This technique provides for a single-stage definitive treatment by affording good intravesical dissection of the ureterocele along with its excision. It facilitates dissection and reimplantation of the refluxing ureters and effectively helps repair the bladder wall and the bladder neck area from where the ureterocele is excised, to achieve a good continence. This endoscopic technique has shown initial results comparable to those obtained with the open technique. Moreover, this technique offers all the advantages of MIS and much faster recovery. The long-term outcome requires follow-up to evaluate the bladder and upper-tract function.[55]

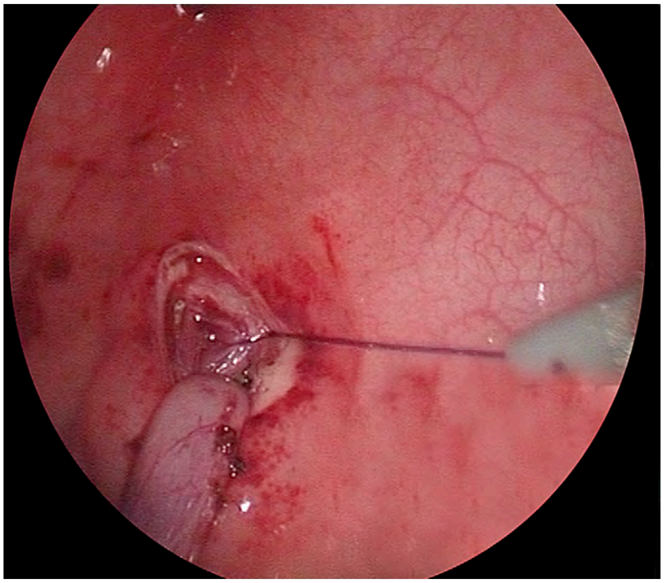


Figure 7-13 Once adequate ureteral length is obtained, the muscular defect in the ureteral hiatus is repaired using 5-0 absorbable sutures, usually with an extracorporeal knot-tying technique.

CRYPTORCHIDISM

Diagnostic laparoscopy has 100% accuracy in determining whether a testis is present in the abdomen and in identifying the various anatomic conditions such as blind-ending cord structures (20%), cord elements entering the internal inguinal ring (45%), testis agenesis (2%), or an intra-abdominal testis (27%).[56,57] Several types of investigations have been used to examine the location of intra-abdominal testes, but consistently there have been reports of missed intra-abdominal testes and lack of specific identification of absent testes.[58] Reports of complex studies such as magnetic resonance angiography reveal a greater sensitivity than conventional studies, but their cost and complexity raise a significant question as to their efficacy.[59,60]

We introduce a 5-mm umbilical port by an open technique for laparoscopic examination of the area around the internal inguinal ring. More recently, very small endoscopes (2 mm) have been used (minilap or needlescopic techniques) directly through the Veress needle to eliminate the need for blind trocar insertion after Veress needle insufflation. The examination of the normal side is done first, to provide an image of the normal anatomic arrangements in the individual patient. The triangular arrangement of the medial vas deferens, lateral spermatic vessels, and iliac vessels should provide a basis for comparison to the opposite side. The obliterated umbilical artery is usually the most readily recognized structure in the area of the internal ring. The vas deferens should cross over it from medial to lateral and course toward the internal inguinal ring. It should then be joined by the

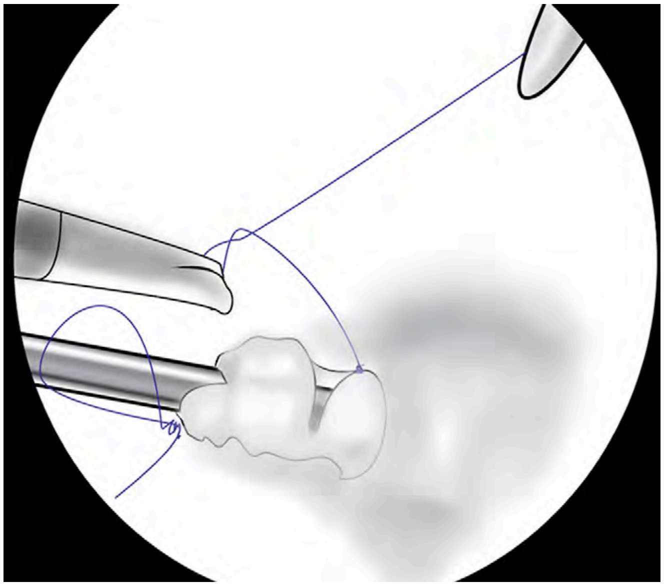


Figure 7-14 Ureteroneocystostomy is performed under endoscopic guidance with intracorporeal suturing using interrupted 5-0 or 6-0 poliglecaprone or polydioxanone sutures.

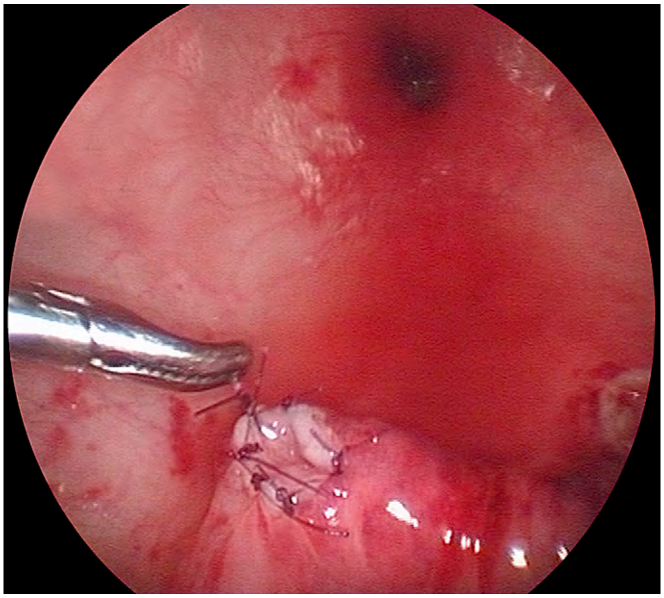


Figure 7-15 Completed ureteroneocystostomy.

spermatic vessels, which may be traced cephalad, running parallel to the iliac vessels. The spermatic vessels are usually a very distinct bundle of vessels. The appearance of the vessels should be noted, because it can indicate the condition of the testis. The internal inguinal ring is usually closed and appears as a flat area of the peritoneum with the vas and vessels passing through it. A patent processus vaginalis may be present, and this is often, but not always, associated with the presence of a testicle. It has been reported that this finding may be used as an indicator that a testis is present in the canal, but this is not always the case, and it provides little practical benefit in management beyond what may be learned from the appearance of the vas and vessels.[61]

During initial examination, after anesthesia, if the testis is palpable high in the canal, laparoscopy may still be used to aid dissection of the intra-abdominal vasculature and vas to prevent the need for an extensive inguinal dissection (Fig. 7-16).[62] If an intra-abdominal vanishing testis is evident by blind-ending vessels, no further intervention is needed, and the procedure is concluded with no incision. If the vas and vessels pass through the internal inguinal ring and are atretic, it is presumed that a vanishing testis is present, and a small, low inguinal exploration is performed at the level of the pubic tubercle. This permits confirmation of the diagnosis with excision of a nubbin of testis.[63] If associated vasal or epididymal anomalies are found or if the testis is very atrophic, with minimal structural attachments, removal may be the best option.[64] We also recommend removal of the testes in children older than 10 years of age. Conversion to a two-stage orchiopexy can be arbitrarily judged by estimating distance of the testicle from the internal inguinal ring and determining a lack of mobility of the spermatic vessels.[65]

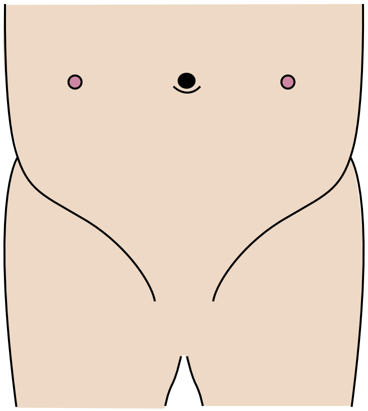


Figure 7-16 Port placement for diagnosis and treatment of nonpalpable testes.

Primary orchiopexy is best performed with 3-mm instruments. Dissection of the spermatic cord and testis is done by incising the peritoneum lateral to the spermatic vessels and extending to the internal inguinal ring. The peritoneum distal to the vas deferens is also incised. This exposes the cord and the gubernaculum. The peritoneal dissection leaves a triangle of undisturbed tissue between the vas and the spermatic vessels, preserving collateral vascularity between them. It also has the advantage of allowing a Fowler-Stephens approach if it is found at the end of the dissection that the vessels still have inadequate length.[66] When the spermatic vessels have been adequately dissected, the testis should easily reach the opposite internal ring. This sign of adequate length is less accurate in older and larger patients, and it is advisable to mobilize more length in an older child. We normally use a 10-mm prescrotal trochar entry for the delivery of the testis into the scrotum. This is done under direct vision from within, along with palpation of the inguinal canal. A laparoscopic grasper is introduced via the scrotum and is used to pull the testis gently to the outside, later to be laid in the subdartos pouch; the skin is then closed with subcuticular stitches.

Surgical Technique: Fowler-Stephens Staged Orchiopexy

This procedure for high intra-adominal testis can be accomplished very well through laparoscopy. In the first stage, the spermatic vessels are clipped with the help of a 5-mm clip applier at a distance of 5 cm from the testes. Use of a needle to introduce a laser fiber for vessel ablation has also been described.[67] We do the second stage 6 months after the clipping of the gonadal vessels. Repeat laparoscopy usually reveals minimal adhesion formation as a result of the initial intervention.[68] The peritoneum is incised widely around the testes and beyond the clipped distal vessels so as to raise a peritoneal flap based on the vas. The gubernaculum is isolated and divided, watching for a looping vas deferens. Length is usually obtained in a straightforward manner, although excessive traction on the vas deferens should be avoided to prevent damage to the fine vessels and to prevent ureteral obstruction.[69]

Treatment described for the very high intra-abdominal testis is by laparoscopically assisted testicular autotransplantation (LATA), which is aided by laparoscopic dissection and microvascular anastomoses. This technique has demonstrated a good long-term surgical outcome and may be used in patients with bilateral intra-abdominal testes and in those with contralateral testis atrophy after unsuccessful orchidopexy.[70]

Results

A series from 10 different centers reported a 97% success rate with a single-stage laparoscopic orchiopexy without division of the testicular vessels.[71] Laparoscopic Fowler-Stephens orchiopexy, with either a single- or a two-stage technique, has also had high success rates. Microvascular orchiopexy showed a high success rate of 80.3% in Docimo's review.[72] More recent series of laparoscopically assisted microvascular anastomoses[70] have demonstrated impressive success, but not higher than that of contemporary series of standard abdominal or staged laparoscopic Fowler-Stephens orchiopexy.

LAPAROSCOPIC VARICOCELECTOMY

Varicoceles are present in approximately 15% of adolescent boys. Varicocelectomy is commonly performed for delayed testicular growth, cosmesis, or symptoms such as pain. Multiple methods exist for the treatment of varicoceles, including percutaneous sclerotherapy and open and laparoscopic surgical ligation of the spermatic vessels. With the recent trend toward MIS, there have been many reports lauding the safety and efficacy of laparoscopy for the surgical correction of varicocele.[73,74]

Surgical Technique

Varicocelectomy can be performed via the transperitoneal route with three trocars or via retroperitoneoscopy with only one trocar.[75] The advantage of retroperitoneoscopy is that it makes the lymphatic vessels clearly visible, allowing the surgeon to spare them and thus reducing the rate of postoperative hydrocele.[75,76] For a left-sided varicocele, we use a transperitoneal approach, with the laparoscope placed through a 5-mm umbilical trocar. Two more ports are placed, one at the level of umbilicus lateral to the rectus and the other in the midline just above the bladder. Sometimes there are adhesions of the sigmoid colon to the peritoneum, covering the varicocele, which must be separated carefully. On visualization of the internal spermatic vessels, the peritoneal reflection is incised in a "T" fashion, and the vessels are dissected out, ligated, and cut between clips or ligatures. Four clips are placed on the vessels, without separately isolating the internal spermatic artery. After hemostasis of the abdominal wall is ensured, the trocars are removed, and the port sites are closed in standard fashion.

Regardless of surgical approach, one of the most frequent complications of varicocelectomy is the formation of hydrocele. The original Palomo repair involved a "high" ligation followed by excision of a segment of the internal spermatic vessels[77]; this procedure was classically associated with a hydrocele rate between 3% and 13%,[78-80] with one study demonstrating a 28% rate of hydrocele formation.[81] Hydrocele formation has been decreased to 0% to 2% in more recent series incorporating microsurgical techniques.[82,83] The difference has been attributed to improved lymphatic preservation with the more meticulous dissection allowed by a low ligation.

INTERSEX

Laparoscopy has been regularly applied to intersex conditions[84] and has also been integrated with operative interventions.[85,86] The intersex states for which laparoscopy is more frequently used are male pseudohermaphrodites, female pseudohermaphrodites, true hermaphrodites, and those with gonadal dysgenesis.[87] Laparoscopy is helpful in gonadal evaluation, resection, or biopsy and for identifying internal ductal derivatives.[88,89] It is also useful for removing all normal structures that are contrary to the assigned phenotype, as well as gonads that are dysgenetic, nonfunctional, malignant, or of increased malignant potential.[85,90]

Laparoscopy gives an excellent view of the pelvic structures and the genital organs. In most cases, identification of these structures is easy and their removal is straightforward. However, the accuracy of identification of the gonads is not total. In some intersex states, the risk for testicular germ-cell tumors is increased more than 100 times, justifying prophylactic gonadectomy as soon as is feasible after the diagnosis is established.[91] The risk of gonadal neoplasia is not confined to patients with a 46,XY karyotype but extends to patients with gonadal dysgenesis and any mosaic karyotype containing a Y chromosome or the SRY antigen.[92]

The male pseudohermaphrodite represents the most frequent indication for therapeutic laparoscopy.[87] Historically, the patient with an underdeveloped phallus has been generally orientated to the female gender, and the testes may be resected. If the testes are palpable, orchidectomy can be done through inguinal incisions, but because most of such patients have impalpable testes, laparoscopic exploration and gonadectomy is indicated.[93,94] If the patient is assigned to or assumes a male role, laparoscopic gonadectomy is still necessary if the gonads are dysgenetic or tumoral, but if the testes are normal, orchidopexy is indicated. In cases of a male pseudohermaphrodite with male gender, resection of müllerian duct derivatives may become necessary.[95] In the rare case of a female pseudohermaphrodite with a male phenotype, laparoscopic gonadectomy with resection of müllerian duct derivatives may be indicated. In the true hermaphrodite with female phenotype, laparoscopic orchidectomy or resection of testicular tissue from the ovotestis is important. In patients who are true hemaphrodites with male phenotype, laparoscopic resection of the müllerian duct derivatives, ovary, or ovarian tissue from ovotestis is indicated, as well as orchidopexy in selected cases. In patients with gonadal dysgenesis, particularly those with a Y chromosome, gonadectomy is essential, whereas resection of müllerian duct derivatives may be indicated in patients with male phenotype.[95]

The laparoscopic evaluation is usually preceded by evaluation of the external genitalia with the patient under anesthesia, to plan the extent of evaluation and the eventual reconstruction in the same procedure. The entire abdomen and the genital area are cleansed and prepared. If combined genitoplasty is planned, the patient is placed in the semilithotomy position. The video cart is positioned at the foot of the patient. The surgical technique includes the classic steps for laparoscopic surgery: peritoneal insufflation through a 5- to 10-mm umbilical trocar for laparoscopic evaluation and two or three additional pelvic trocars for therapeutic procedures. The gonadal structures are evaluated carefully. In some cases in which the gonads are not easily seen, the gonadal vessels may be identified and followed downward. Most often, the gonads are identified near the inguinal region; they may have a normal testicular or ovarian appearance or a dysplastic or tumoral aspect. In some cases, the gonads are not clearly identified because of dysplasia, leading to confusion with ductal structures. Once identified, the gonads are resected, most often together with the ductal structures. In the presence of a normal testis in a patient with a male phenotype, laparoscopic orchidopexy can be performed.[84]

LAPAROSCOPIC VAGINOPLASTY

Construction of an artificial vagina has undergone a long evolution. Zangl,[96] in 1955, and Pratt,[97] in 1961, proposed the use of sigmoid colon in vaginal reconstruction. Today, most surgeons favor a technique in which a pediculated isolated sigmoid colon segment is used.[98-100]

The experience with a laparoscopic approach is limited for vaginal reconstruction.[101,102] The procedure is conducted with the patient under general anesthesia and placed supine on an operating table with stirrups, such as that designed for perineal surgery. After insertion of a vesical catheter, laparoscopic ports are placed. A 10-mm trocar is placed below the umbilicus, and the pneumoperitoneum is created. The second, 12-mm port is inserted on the right side, midway between the iliac spine and umbilicus. At the corresponding contralateral site, a 5-mm port is inserted. A 14- to 17-cm long, vascularized sigmoid segment is isolated using a harmonic scalpel and a 12-mm endoscopic gastrointestinal stapler (Endo GIA) stapler.

Next, with the patient's legs placed in lithotomy position, the perineal stage of the procedure is begun by the creation of a U-shaped incision at the deepest depression at the vaginal opening. Under laparoscopic guidance, a surgical plane is developed between the urethra, bladder, and rectum, reaching down to the pelvis to form a canal two fingers wide. Through the created space, a clamp is introduced with a gauze pad placed at the tip, and the site for incising the peritoneal fold in the region of the hypoplastic uterus is selected under visual control. The incision is performed using a hook cautery to produce an opening sufficient to allow free passage of the isolated sigmoid colon segment. Subsequently, the clamp is used to bring the distal end of the sigmoid through the canal, down to the level of the incised margins of the vestibule of the vagina. The open proximal end of sigmoid in the abdominal cavity is closed with intracorporeal suturing or with the Endo GIA stapler. Gastrointestinal continuity is re-established with the use of a circular endoscopic stapler. The external reconstruction is completed, resulting in a normal appearance of the vulva.

PROSTATIC UTRICLE

The prostatic utricle, an enlarged diverticulum in the posterior urethra of males, was first described in 1874.[103] Although most prostatic utricles are asymptomatic, they may manifest with symptoms as a result of their size or infection (Fig. 7-17). Utricles have been associated with recurrent urinary tract infections, stone formation, disturbed urination, recurrent epididymitis, infertility, and neoplastic degeneration.[104-107]

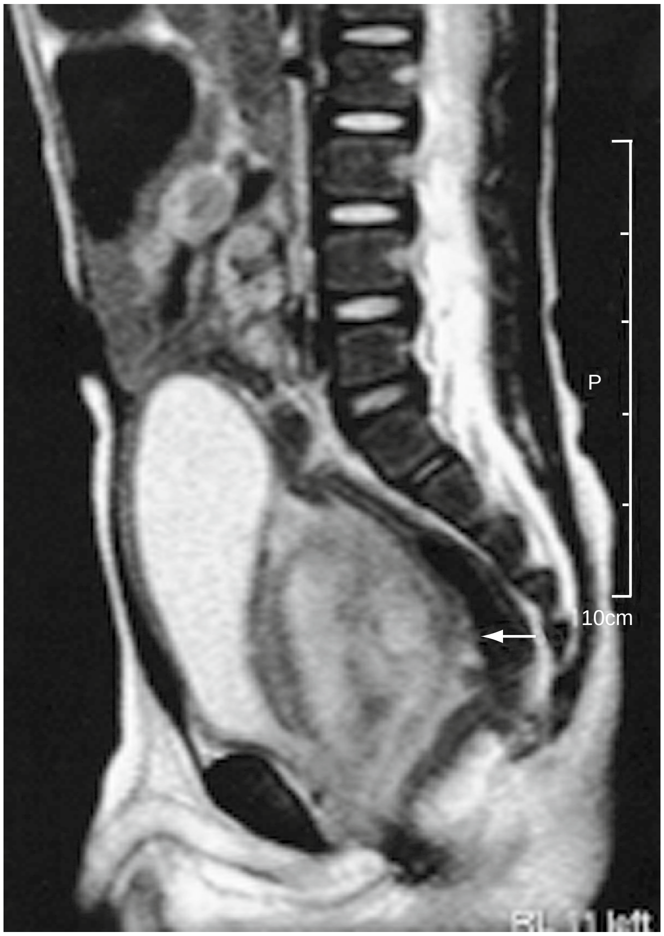


Figure 7-17 Magnetic resonance image showing a large prostatic utricle *(arrow)*.

The prostatic utricle, also known as a müllerian duct cyst, is an embryologic remnant that results from a transient decline in fetal testicular function during the critical period of urethral formation, in the 9th to 10th week of fetal life.[108,109] The effect of a decline in either hormonal output or hormonal sensitivity of the tissues, at the stage when the urogenital plate is formed from the fused tips of the müllerian duct as they come into contact with the urogenital sinus, results in formation of the prostatic utricle.[110] The incidence of an abnormally enlarged prostatic utricle in the male population is reportedly 14% of patients with proximal hypospadias and 57% in patients with perineal hypospadias.[111] The incidence of prostatic utricle has been reported to be increased with increasing severity of hypospadias.[106,108,110]

Surgical excision has been the recognized treatment of choice to treat the problems arising from this condition. We use laparoscopy for excision of the prostatic utricle.[112,113] Laparoscopy offers a clear and close view of the bladder base and the prostatic utricle. With the patient under general anesthesia and in the lithotomy position, cystourethroscopy is undertaken and the prostatic utricle is cannulated. The cystoscope is left in situ inside the prostatic utricle to facilitate subsequent identification and mobilization during laparoscopy via a 5-mm port inserted through a supra-umbilical incision. Two more 3- to 5-mm working ports are inserted at the right and left midabdomen. The bladder dome is hitched upward to the anterior abdominal wall by a 4-0

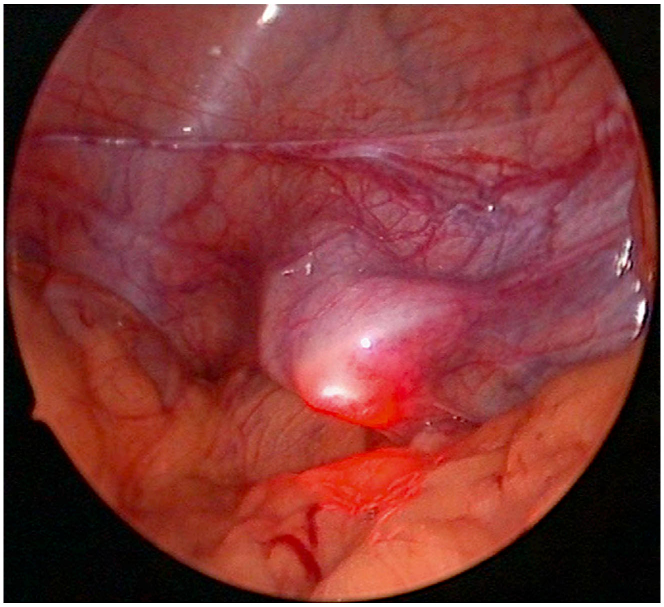


Figure 7-18 Laparoscopic view of the prostatic utricle under cystoscopic guidance.

polydioxanone suture inserted percutaneously under laparoscopic vision. The peritoneal reflection is incised using electrocautery, starting immediately behind the bladder. The prostatic utricle is easily identified with the guidance of illumination from the cystoscope (Fig. 7-18). Dissection is further facilitated by lifting and countertraction of the prostatic utricle by an assistant using the indwelling cystoscope. Both ureters are clearly visualized laparoscopically and protected throughout the course of dissection. A 5-mm ultrasonic scalpel is used to completely mobilize the prostatic utricle and divide it at its confluence with the urethra. The urethral defect is closed by intracorporeal suturing with the use of fine absorbable sutures. The excised prostatic utricle is removed through the supra-umbilical camera port. In our series, laparoscopic excision of the prostatic utricle was successful in all four patients, and none had any voiding difficulties.

MINIMALLY INVASIVE SURGERY IN INCONTINENCE

One of the important developments in surgery for neurogenic incontinence has been the application of minimally invasive techniques, either as assisted reconstructive procedures or for pure laparoscopic or robot-assisted procedures. Procedures such as laparoscopic enterocystoplasty, laparoscopic ureterocystoplasty, laparoscopic–bladder neck reconstruction, and laparoscopic autoaugmentation have earned a place in the treatment of incontinence in children.

Laparoscopically Assisted Reconstructive Surgery

At the moment, the state of the art for minimally invasive reconstruction mainly involves laparoscopically assisted methods. The principle of laparoscopically assisted reconstructive surgery is to use laparoscopy to perform the parts of the operation that require upper abdominal access and to do the technically demanding reconstructive steps through an open lower abdominal incision.[114] Laparoscopically assisted surgery is widely applicable for patients who require bladder reconstruction or antegrade continence enema stoma, or both. Most of the patients reported in the literature have had prior abdominal surgery, including ventriculoperitoneal shunt placement and bladder exstrophy closure.[114,115] The benefit of laparoscopic mobilization is cosmetic; it results in more rapid recovery and decreased intra-abdominal adhesions.

Laparoscopic Enterocystoplasty

The first laparoscopic gastrointestinal bladder augmentation was performed using stomach.[114] The laparoscopic technique involves the use of endo clips to dissect the gastroepiploic pedicle and endoscopic gastrointestinal anastomotic staplers to excise a wedge of stomach. Laparoscopic bladder augmentation has also been performed with the use of small or large intestine, usually with an extracorporeal bowel anastomosis.[116] The initial experience suggests that laparoscopic enterocystoplasty has the potential to become a viable alternative to open enterocystoplasty. Laparoscopic enterocystoplasty successfully emulates the established principles of open enterocystoplasty while minimizing operative morbidity, although it is currently a lengthy procedure, lasting twice as long as open surgery. Further technical modifications and increasing experience will continue to reduce the surgical time involved.

Laparoscopic Ureterocystoplasty

Laparoscopically assisted ureterocystoplasty is an appealing MIS technique, because small kidneys are easily amenable to laparoscopic mobilization followed by the ureterocystoplasty through a cosmetically acceptable Pfannenstiel incision.[117] The mobilization of the renal unit can be transperitoneal or extraperitoneal, with 3- and 3.5-mm instrumentation. In our approach, the upper ureter is completely mobilized in the retroperitoneal cavity to the level of the iliac vessels. The patient is then repositioned supine for a Pfannenstiel incision, through which the mobilized kidney and ureter are accessed. A standard ureterocystoplasty, using the entire ureter and pelvis, is then performed.

Laparoscopic Bladder Neck Reconstruction

With the development of the pneumovesical approach to intravesical surgery, it is now also possible to perform a bladder neck reconstruction. The intravesical technique of bladder neck reconstruction via a pneumovesicum described here is a modified reverse Kropp procedure.[118-120] Intertrigonal posterior mucosal tubularization is combined with the creation of a flap-valve mechanism by apposition of the undermined mucosal edges lateral to the neourethra in the midline. The procedure has been further modified by tightening of the anterior half of the bladder neck and the proximal 1.5 cm of urethra, which further secures a competent bladder neck. Loss of functional bladder capacity by this procedure is minimal, and the technique provides an excellent close-up view of the bladder and its neck for performance of the reconstruction.

Surgical Technique

Two parallel incisions are made about 1.5 cm apart, along the posterior wall of the bladder extending from the anterior bladder neck to the level of the interureteric bridge, using monopolar diathermy (Figs. 7-19 and 7-20). The incision is deepened to expose the detrusor muscle in the bladder neck area.

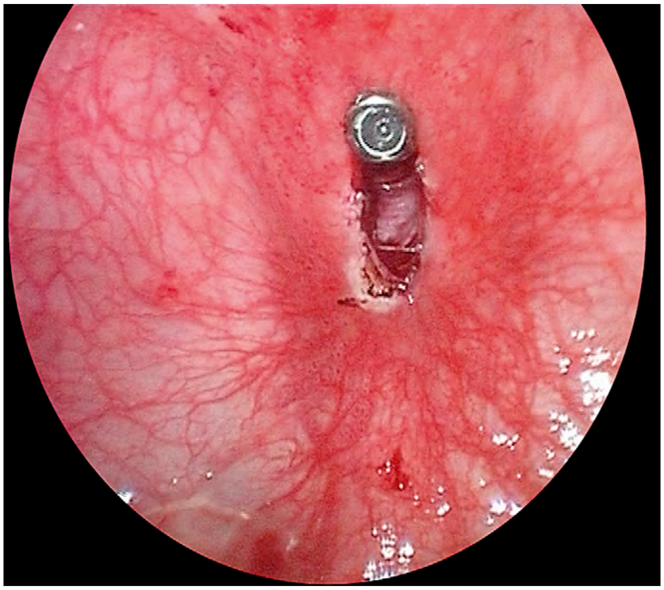


Figure 7-19 Vesicoscopic view of the bladder neck.

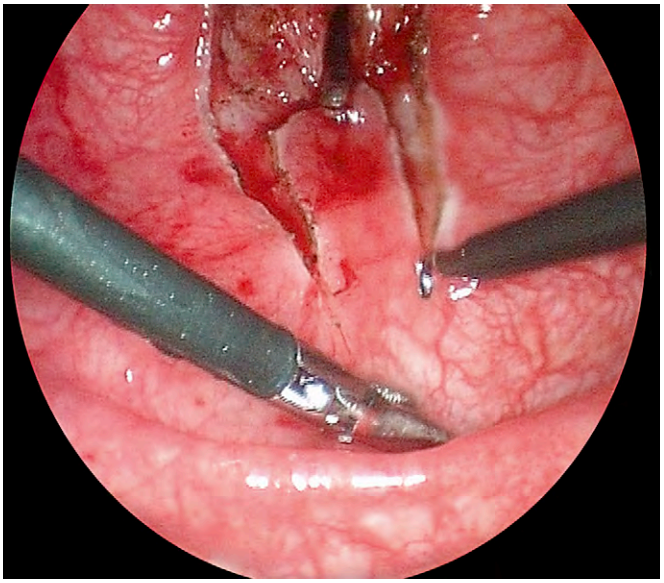


Figure 7-20 Two parallel incisions are placed along the posterior wall of the bladder extending from bladder neck to the interureteric ridge.

A urethral stent is advanced through the bladder neck, and the bladder neck is narrowed by closing the anterior rim over the stent using interrupted 5-0 Biosyn monofilament absorbable sutures. The rest of the mucosal strip is then mobilized on both sides with the aid of 3-mm scissors and hook cautery. The mucosal strip is tubularized around the stent with the use of 5-0 interrupted absorbable sutures. The mucosal edges lateral to the tubularized neourethra are then dissected free laterally so as to achieve a tension-free closure over the tubularized strip using Biosyn 5/0 interrupted stitches (Fig. 7-21). In addition to the urethral stent, a 10F (3.3-mm) suprapubic catheter is left in situ for postoperative drainage of the bladder. The suprapubic catheter is placed via the supraumbilical port site, and the port is removed. The length of suprapubic catheter inside the bladder can be adjusted under laparoscopic guidance. The rest of the ports are removed, and the bladder defects are closed by tying the preplaced sutures. Local anesthesia over the port sites is optional. The skin wounds are further closed with a 5-0 subcuticular absorbable monofilament suture. We have done transvesicoscopic bladder neck reconstruction with urethral lengthening successfully in five patients. The mean operating time was about 3 hours. Four patients have achieved complete continence.[121]

Laparoscopic Autoaugmentation

Autoaugmentation, or detrusorraphy, is a technique that involves dividing the bladder muscle and dissecting it free of the mucosa.[122] This allows the development of a large bladder diverticulum, which results in improved compliance and low-pressure storage. Because this is a form of bladder augmentation that does not involve the harvesting of gastrointestinal segments and requires very little suturing, it is adaptable to minimally invasive techniques. Laparoscopic autoaugmentation has been performed in animal models[123] and in children,[124-126] by both a transperitoneal and an extraperitoneal approach.[127] Bladder autoaugmentation requires a large incision of the detrusor with dissection of the underlying mucosa over a large surface area, often followed by fixation of the bladder muscle to the pelvic sidewall to prevent narrowing of the mouth of the newly formed bladder diverticulum. The process of separating bladder muscle from mucosa has been assisted with laser, with the theoretical advantage of a limited depth of tissue destruction.[125] This operation can be done with a very short hospital stay or on an outpatient basis, but it does require postoperative bladder drainage for some period because of the possibility of rupture and leakage.

Long-term results of open or laparoscopic autoaugmentation have not been consistent,[128] and autoaugmentation has not achieved wide acceptance as a reconstructive technique in children. This is, however, a minimally invasive technique of bladder enlargement, and it may be considered for patients who have reasonable capacity but poor compliance and for those who do not require a large increase in bladder capacity.

Mitrofanoff Appendicovesicostomy

In recent years, several investigators have successfully incorporated laparoscopy into the pediatric urology reconstructive procedure to minimize postoperative patient morbidity and improve cosmesis.[114,129-133] Pedraza and colleagues reported on a robotically assisted laparoscopic Mitrofanoff procedure.[134] Laparoscopic Mitrofanoff appendicovesicostomy is performed using a transperitoneal, three-port approach. After the initial access to the peritoneal cavity at the umbilicus using the Hassan technique, in which a 10-mm trocar is placed, two additional trocars are placed: a 12-mm trocar along the lateral border of the left rectus muscle at the umbilical level and a 5-mm trocar along the lateral border of the right rectus muscle at the umbilical level. With laparoscopic visualization, the appendix is identified. The right colon is mobilized medially. The appendix is separated from the cecum, leaving a small cuff of cecum with the appendix; this facilitates the stomal anastomosis and decreases the risk of stenosis. The cecum is closed in two layers. The appendix can be harvested with the use of the Endo GIA stapler, including a 5-mm cuff of cecum, with preservation of the mesentry and the vascular supply. The cecal staple line is oversewn in two layers with 4-0 silk suture, using laparoscopic intracorporeal freehand suturing and knot-tying techniques. The native bladder is then identified with the aid of carbon dioxide insufflation at 12 to 14 mm Hg by way of an indwelling urethral catheter.

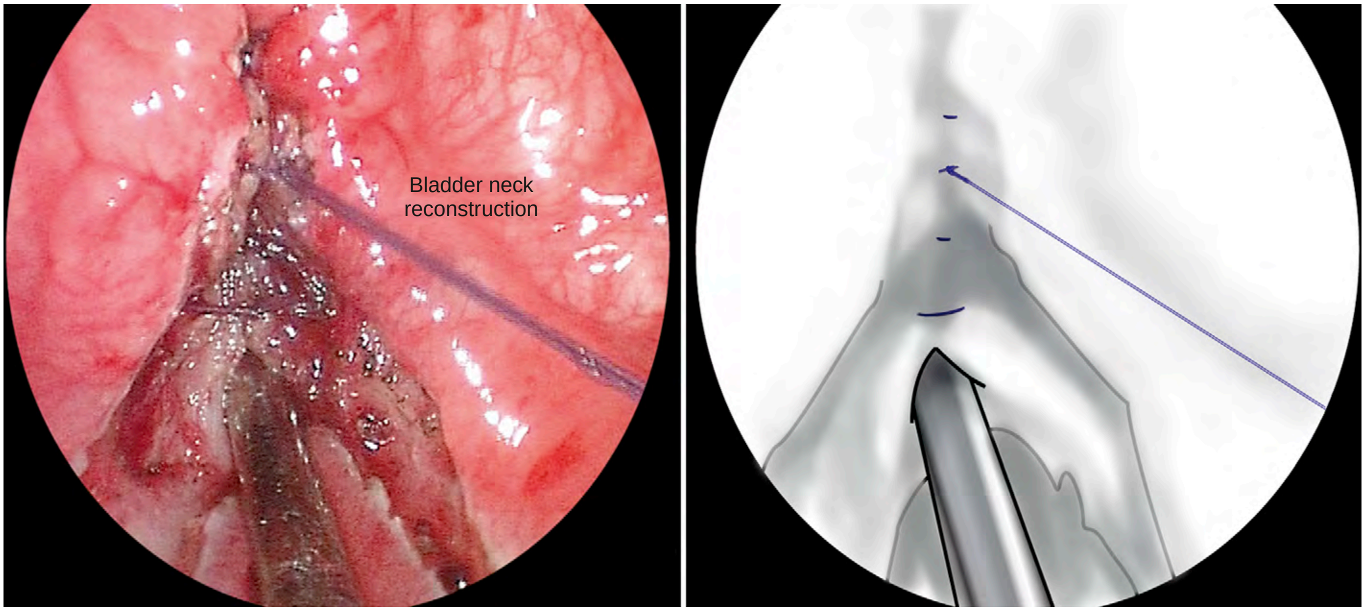


Figure 7-21 Tubularization of the incised strip over a catheter. The tube is closed in two layers using 5-0 absorbable sutures.

A 5-cm detrusor muscle trough is created along the right posterolateral aspect of the bladder, after which a small cystotomy is created at the distal end of the trough. The distal 5 mm of appendix is excised and spatulated, revealing a 1-cm lumen. The appendiceal-vesical anastomosis is then performed circumferentially with eight interrupted stitches using 5-0 polyglycolic acid sutures. Next, the distal 5 cm of appendix is placed in the newly prepared detrusor muscle trough, after which the detrusor muscle edges are approximated over the appendix with interrupted 4-0 polyglactin sutures, maintaining at least a 5:1 ratio of trough length to tube diameter. Care is taken to ensure absence of twisting or tension on the appendiceal mesentery. All reconstructive maneuvers are performed using laparoscopic intracorporeal freehand suturing and knot-tying techniques. The base of the appendix is brought up to reach the umbilicus without tension, and a catheterizable stoma is created using a V-flap technique.

The bladder is filled with 200 mL of saline to check for any leak from appendiceal-vesical anastomosis. Continence and ease of catheterization are also checked and confirmed intraoperatively, after which a capped 10F Foley catheter is placed through the appendiceal conduit into the bladder. Under laparoscopic guidance, a puncture suprapubic tube can also be placed percutaneously. In our experience, the overall clinical outcome of the present laparoscopic technique appears to be satisfactory. Despite this preliminary success, additional clinical experience is necessary to define its role further.

Laparoscopic Antegrade Continence Enema Procedure

The antegrade continence enema (ACE) was first described in 1990 by Malone and associates.[135] It is used for intractable fecal incontinence and constipation of various causes, mostly in patients with spina bifida and associated neurogenic bowel. It has been demonstrated to be safe and effective and has a high success rate.[135,136] However, the procedure is not without significant potential problems, such as stomal stenosis, stomal prolapse, and stool leakage.[137] The use of laparoscopic techniques in construction of an ACE channel is evolving as a minimally invasive procedure that attempts to address issues of morbidity commonly associated with the technique.[137-140] The current laparoscopic antegrade continence enema (LACE) mechanism has relied on the length of the appendix and the appendicocecal sphincter.[137] LACE approaches are described as involving either laparoscopic assistance or a total laparoscopic approach.[137-143]

Surgical Technique

The patient is placed supine. A three-port transperitoneal approach is used, with the initial 10-mm port placed at the inferior umbilical crease. Insufflation to an abdominal pressure of 12 mm Hg is established. A second port (10 mm) is placed at McBurney point. A third port (5 mm) is placed in the midline below the level of the umbilicus. The surgical table is positioned so that the patient is in a 45-degree Trendelenburg position with a 45-degree lateral rotation so that the ipsilateral side is exposed. The small bowel is manipulated medially, and the cecum is identified. Once confirmation of an adequate appendix has been obtained, the cecum is mobilized from its attachments to the body wall with cautery. The colon is mobilized approximately one third of the distance toward the hepatic flexure, just enough to allow mobilization of the cecum to the anterior abdominal wall during insufflation.

The appendiceal mesentery is freed with sharp dissection and hook electrocautery at the base of the cecum, avoiding injury to the appendiceal artery. The serosa at the appendicocecal junction is incised along the tinea, leaving the mucosal lining intact. Then, 3-0 silk is used to imbricate the serosa onto the appendix, reinforcing the valve mechanism. The appendix is grasped with an endoscopic Babcock clamp and delivered through the umbilical port. The abdomen is desufflated. The tip of the appendix is transected and cannulated with an 8F (2.64-mm) pediatric feeding tube to verify patency. The feeding tube is left indwelling. A skin flap is fashioned in a "V" configuration at the umbilicus, incorporating the incision made for the port. A stoma is created with this flap through the existing fascial defect of the 10-mm port. The feeding tube is removed and reinserted through the stoma to ensure patency and ease of passage. The cecum is then irrigated to verify continence. The feeding tube is reinserted and secured to the abdominal wall. After the appendix has been externalized, the abdomen is insufflated once again. The cecum is fixed to the right anterolateral abdominal wall with 3-0 intracorporeal polyglactin sutures.

Appropriate patient selection is of paramount importance in the success of the LACE procedure. It has been reported that patients with spina bifida and those with rectal or anal incontinence have better success with this procedure than do patients who are chronically constipated.[140] A relative contraindication, as in most elective surgical cases, would be any indication of noncompliance. Longer follow-up and more cases are needed to assess continence with the laparoscopic technique.

COMPLICATIONS OF PEDIATRIC LAPAROSCOPY

The complications in children can be divided into those related to the access and those associated with pediatric laparoscopy.

Complications Related to Access

The Veress needle access technique is associated with preperitoneal insufflation caused by tenting of a poorly attached peritoneum during the entry. During the primary port insertion, after insufflation, one may need to push harder because the tip of the trocar is not yet visible in the field, but makes puncture of abdominal viscera more likely. During retroperitoneal procedures, the peritoneum is more easily violated, because of its more posterior reflection; it is thin and weak in strength. This can occur even with excessive inflation of a balloon dissector. The open access technique is safer but not without hazard, including inadvertent injury to a loop of bowel trapped during the opening.[144]

Intraoperative Complications

The cause of intraoperative complications in pediatric laparoscopy is most often the use of instruments that are inappropriately sized relative to the available limited working space, which is the case in most small children. It is therefore crucial to use the correct small-size instruments. All of the 3- and 3.5-mm pediatric laparoscopy instruments are available in 20- and 30-cm lengths. Extra care is needed when operating in confined space. With smaller telescopes, vision gets compromised easily by smoke, fluid, and light absorption due to blood. All instruments must be exchanged with greater care, because the safe range of movement is usually less. Smaller-diameter working instruments increase the risk for electrical effects because the current density is higher, and with thinner abdominal walls the current dissipates less efficiently.[144,145] It is a good practice to always test the insulation and the optimum current needed during a particular surgery, to minimize electrocautery-induced injury.

The effect of pneumoperitoneum on ventriculoperitoneal shunt function has been an issue. However, clinical experience has not confirmed these concerns, and numerous procedures have been performed without ill effect. With a functioning valve in the shunt, there should be no risk of increasing intracranial pressure.[146]

Complications of Carbon Dioxide Pneumovesicum Procedures

Work in the bladder is limited by the small space that is available after port placement, although the success of this procedure is aided by the small-sized instruments and excellent endoscopic vision. We have not faced any major complications in this technique. In the early part of the series, when the cannulas were not secured to the bladder wall, displacement of the port outside the bladder wall occurred. This resulted in gas leakage into the extravesical space, with compromise of the intravesical space and endoscopic vision. It is usually possible to reintroduce the ports, but securing the ports perfectly is the key to the success of this technique.[53,54] We have observed mild to moderate scrotal and suprapubic emphysema immediately postoperatively, which subsided spontaneously within 24 hours. Persistent mild hematuria up to 72 hours has also been observed and also settles spontaneously.

ROBOT-ASSISTED LAPAROSCOPY

Robot-assisted laparoscopy has provided an opportunity to apply new techniques to practice MIS. We believe that one of the main advantages of the robotic system, especially in children, is that it offers surgeons who are inexperienced in laparoscopy the benefits of high dexterity in minimally invasive procedures, as well as allowing the experienced laparoscopic surgeon to improve his or her capability.[147] Robot-assisted laparoscopy has complemented and helped to overcome some of the limitations of laparoscopic techniques, particularly for pediatric reconstructive surgeries.[148,149] The da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA) provides the advantage of three-dimensional visualization with tremor-filtered instrument movement and articulating instruments with six degrees of freedom to perform delicate manipulations for reconstructive surgery.[150]

Robot-assisted laparoscopic nephrectomy, nephroureterectomy, and partial nephroureterectomy are well-established procedures in children, although they do not use the advantage of any reconstruction techniques provided by the robot. Upper tract procedures can be performed using transperitoneal or retroperitoneal approaches, but the transperitoneal operation is most readily accomplished because of the favorable relation between the available operative space, the size of the ports, and the arms. The choice of a transperitoneal or a retroperitoneal approach depends on the surgeon's experience and the need for additional procedures, such as removal of the entire ureter, or concurrent procedures, such as intra-abdominal testicle or ureteral reimplantation. Retroperitoneal access is distinct in port placement and patient positioning. Ports are placed posteriorly or laterally, depending on surgeon preference. The size of the robotic arms makes a posterior approach more difficult except in bigger-sized children. The initial dissection uses either a balloon or blunt dissection under direct vision to develop the retroperitoneal space.

Laparoscopic pyeloplasty in children and neonates requires precision; it is technically challenging and is a potentially lengthy procedure because of the high proficiency level required for intracorporeal suturing. With experience, operative times have been shown to improve, as with open procedures. Robot-assisted laparoscopic pyeloplasty can be performed with either transperitoneal or retroperitoneal access and offers the advantage of using smaller suture material, as fine as 7-0. Several experiences with robot-assisted laparoscopic pyeloplasty have demonstrated improved surgical dexterity by providing precision in dissection, incision, and suturing, as well as decreased operative times. For a transperitoneal approach, the anesthetized patient is placed in supine position and secured to the table, with a 30-degree wedge cushion. The ports are placed in the umbilicus for the camera port, in the midline between the umbilicus and xyphoid for one working port, and in the midclavicular line below the umbilicus for the other working port. The patient is turned to 60-degree elevation of the ipsilateral side after port placement, and the robot is brought in over the ipsilateral shoulder for docking. The surgical steps principally remain the same as previously discussed (see Laparoscopic Pyeloplasty). Various surgeons have reported success rates similar to those obtained with the "gold standard" open procedure, about 95%.[151-153]

We perform the Anderson-Hynes pyeloplasty repair using the da Vinci robot mainly by a transperitoneal approach. The robot allows us to deal with intrinsic problems, which are easily excised and repaired. Extrinsic issues, such as crossing vessels, are readily addressed. We have seldom used this technique in children younger than 1 year of age. Our initial results in children older than 1 year have been comparable to those of laparoscopic pyeloplasty, although the 8-mm robotic instruments were discovered to be too big for a small child, compared with the 3-mm instruments we use in laparoscopy.

The robot-assisted extravesical approach for treating VUR can be performed unilaterally or bilaterally, following the same steps as described earlier. Typically, the patient is in the supine position and the legs are placed apart. An open technique is used to place the first trocar, the 12-mm camera port, in the umbilicus. The working ports (8 mm) are positioned in the midclavicular line bilaterally, about 1 cm below the umbilical line. Ports are fixed and secured firmly to the abdominal wall using a stitch that is also used to close the fascia later. The robot is docked over the child's feet end to perform the surgery.

For the robot-assisted Cohen procedure, the patient and the robot docking position are same as described for the extravesical approach. The major difference compared to the conventional laparoscopic Cohen procedure is that a robot-assisted procedure uses a 12-mm camera port and two 8-mm working ports. Our initial experience with the da Vinci robot has been far from satisfactory. Based on our working space model and collision study model, we have recognized that smaller working space is a major limitation on the performance of complex reconstructive tasks using the da Vinci robot without collision.[154,155]

The major reconstruction applicability of the da Vinci system has been to do a pyeloplasty. A variety of other procedures have been performed using robotic assistance for laparoscopic surgeries in children, including ureteral reimplantation,[156] Mitrofanoff technique,[134] Mitrofanoff with MACE procedure using divided appendix,[121] as well as pyelolithotomy, adrenalectomy, bladder neck sling, pyeloureterostomy, and excision of müllerian duct remnants. In all cases, the procedure could be completed with surgical success. It is difficult to accurately assess the impact on reduction of morbidity, but overall, the enhanced visualization and dexterity are noticeable.[149,156]

Disadvantages of this robotic system include the lack of tactile sensation; therefore, visualization of anatomic landmarks is the key to successfully completing the operation. The unscrubbed surgeon is away from the operating table and must depend on an experienced, scrubbed assistant. Active communication among the primary surgeon, first assistant, and staff is imperative. Although the learning curve for the surgeon may be short, there is a substantial learning curve for the ancillary staff. Finally, the cost of the da Vinci robot is always a consideration. An initial investment of more than $1,000,000 and subsequent running costs of $80,000 to $100,000 per year may make this procedure unfeasible at many centers. Robotic surgery in pediatric urology is an evolving technique. The computer-assisted system has introduced smaller instruments (5 mm), which are available but do not provide any added advantage in efficiency, primarily due to its design and the monocular lens system. Other improvements in design have been the addition of a fourth arm, which can be applied as a retractor, and the development of a smaller robot with better maneuverability while docking. As the technology continues to get better, the efficiency of the robotic system is likely to improve and offers the means to overcome impediments to surgery in children. Animal studies demonstrate that robotic assistance can increase the applicability of MIS to complex procedures in children and neonates[157]; however, the ultimate role of robot-assisted or computer-assisted surgical systems remains unclear.

CONCLUSION

There has been a continued expansion in the application of laparoscopy in the pediatric population. Improvements in optics and instrumentation and the use of robotic assistance have brought new dimensions to the use of MIS in the pediatric population. Laparoscopy has provided a unique opportunity for pediatric urologists to work in a small space around and inside the urinary bladder. It has also allowed exploration of the complete urinary system, from the kidneys to the urinary bladder, with just a rotation of axis of trochars holding the laparoscope and the working instruments, thus aiding in dealing with all the major pediatric urology surgeries in a minimally invasive fashion. Smaller scars, less pain, and quicker recovery are all potential benefits of laparoscopy, but there is also a potential for causing harm if the application of minimally invasive technique is not done properly, particularly because of the lack of adequate experience in this field. Technically, most complex reconstructions in children have been achieved with the use of laparoscopic technique, but their reproducibility has yet to be proved, as well as whether their long-term outcome is comparable to that of the established open technique. It is therefore important to have proper clinical trials that can objectively evaluate the use of these technically demanding techniques in children.

REFERENCES

For complete list of references log onto www.expertconsult.com

SECTION 3

FUNCTIONAL INVESTIGATIONS

CHAPTER 8

RADIOISOTOPE IMAGING OF THE KIDNEY AND URINARY TRACT

Lorenzo Biassoni and Isky Gordon

Radioisotope investigations are used to estimate the contribution of each kidney to total renal function, to look for focal functional abnormalities of the renal cortex, to provide an evaluation of drainage, and to assess for the presence of vesicoureteric reflux (VUR). Bladder function in terms of timing and completeness of bladder emptying can also be studied by isotope techniques. The strength of nuclear medicine is the ability to quantify physiology and to allow continuous monitoring of a parameter over time. The weakness is its poor anatomic detail, and for that reason, close correlation with morphologic imaging is essential for a correct interpretation of the results. The nuclear medicine examinations available to image the urinary tract give a relatively low radiation burden but, as with all radiologic investigations in pediatrics, their use has to be clinically justified: the principle of administering the lowest possible radiation dose to answer the clinical question is of paramount importance in pediatric radiology.

Applications in nephrourology constitute about 50% to 60% of the workload of a pediatric nuclear medicine unit. The practice of pediatric nuclear medicine is technically more difficult than adult nuclear medicine. A child is not simply a small adult. It is essential that the pediatric nuclear medicine team be child friendly. Winning the child's and the parents' cooperation is the key to a successful examination. The nuclear medicine team has to be keen and trained to work with children. The goal for a technician or radiographer is to have the child remain still on the gamma camera couch during acquisition of the images. This is obtained by making the child and parents feel at ease before and during the examination. Kindness, clarity, and honesty in explaining what the different parts of the examination are and what they entail are extremely helpful in winning the parents' and the child's cooperation. The child must be immobile during the examination: for this purpose, sandbags and Velcro straps are useful. Anesthetic cream is applied to arms, hands, and sometimes feet to minimize the pain during venous cannulation. Adequate hydration before tracer injection is very important, both to facilitate excretion of the tracer (thus minimizing the radiation burden) and, in the case of dynamic renography, to allow good visualization of drainage through the collecting systems and ureters.

Good acquisition of images reduces the possibility of pitfalls. However, some pitfalls always occur, and these must be well known by the reporting radiologist. The radiologist/nuclear medicine physician must have a good knowledge of the clinical scenarios and the queries faced by the urologist. These are often very different from the clinical questions posed to the radiologist in adult urology.

Other radiologic techniques, such as magnetic resonance imaging (MRI), are making rapid progress. In the near future, gadolinium-enhanced diethylenetriamine penta-acetic acid (Gd-DTPA) MRI may be able to provide the differential renal function as well as time-signal curves and possibly the absolute glomerular filtration rate (GFR), coupling this information with superb anatomic resolution and no radiation burden.

STATIC CORTICAL SCINTIGRAPHY

Tracers

The tracer used for static cortical scintigraphy is technetium 99m (Tc^{99m})-labeled dimercaptosuccinic acid (DMSA). It binds to the renal proximal tubules, resulting in an unchanging fixation of the tracer in the kidney over the following hours. (It is still possible to acquire a DMSA scan 24 hours after tracer injection.) Ten percent of the injected activity is excreted into the bladder. An alternative tracer is Tc^{99m}-glucoheptonate, which is partly bound to cortical renal tubules. However, the cortical uptake is significantly reduced in comparison to Tc^{99m}-DMSA, with 40% to 65% of the isotope being excreted into the bladder via the urine.

Acquisition Technique

Sedation of the child is only rarely necessary. A suitable environment, an adequate attitude toward the child and parents, a well-trained radiographer/technologist for pediatric procedures, and well informed parents who are involved before and during the procedure provide effective circumstances to obtain adequate immobilization of the child during the acquisition. The most difficult age is between 1 and 3 years; in this age group, sedation may be very occasionally required. The safest drug is midazolam (intranasal or per rectum), which helps reduce extreme anxiety.

It is envisaged that, because the clinical relevance of a small scar seems negligible,[1] DMSA single-photon emission computed tomography (SPECT) will be performed only very seldom.

A DMSA scan gives a radiation burden of approximately 0.9 mSv, regardless of the child's age, provided that the injected dose has been adjusted to body surface area. This exposure is not insignificant, and care should be taken to make sure that all possible information is extracted from the scan. The best possible image quality should be sought. In a high-quality DMSA study, it should be possible to clearly distinguish the relatively hotter cortical columns of Bertin from the cooler medulla and collecting system (Fig. 8-1).

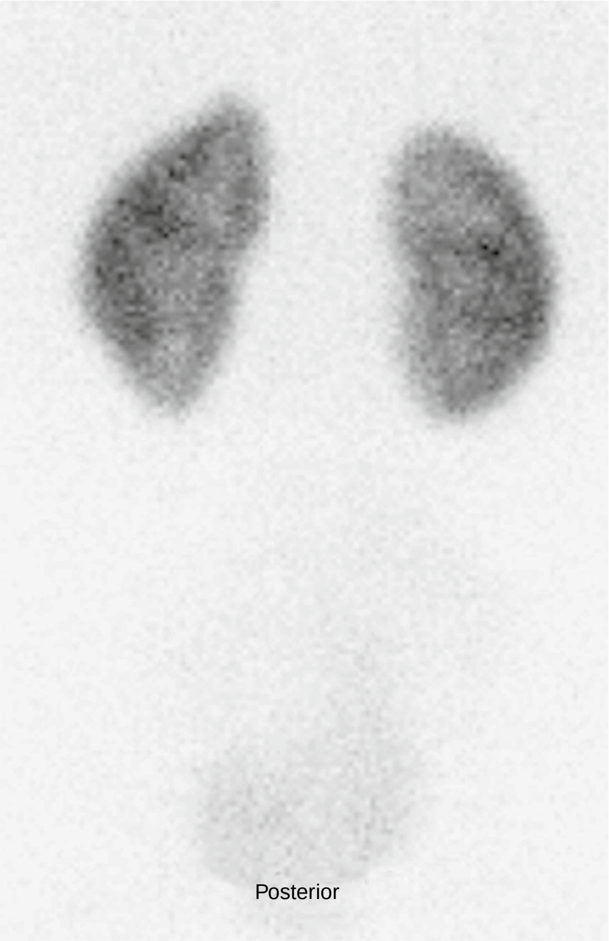


Figure 8-1 Normal static cortical scintigraphic scan using technetium 99m–labeled dimercaptosuccinic acid (^{99m}Tc-DMSA). Approximately 48% of function is in the left kidney and 52% in the right kidney. Note the high-quality images with good definition of the internal renal architecture. A high-resolution collimator was used for the acquisition.

Table 8-1 Indications for a DMSA Scan

Detection of focal parenchymal abnormalities
Detection of acute pyelonephritis
Detection of renal scars after a urinary tract infection
Detection and relative function of an ectopic kidney
Detection of an ectopic kidney not found by ultrasound
Detection of a duplex kidney with ectopic drainage in a constantly wet child
Follow-up of a chronic pyelonephritis
Evaluation of relative renal function of a kidney with gross dilatation
Evaluation of regional renal function in a child with congenital renal abnormalities

DMSA scan, static cortical scintigraphy using technetium 99m–dimercaptosuccinic acid.

Table 8-2 Normal Variants of a DMSA Scan

Flat contour
Splenic impression on the lateral aspect of the superior portion of the left kidney
Triangular kidney
Slender kidney, with a short transverse axis in the posterior view (rotated kidney)
Pear-shaped kidney (with a shorter transverse axis at one pole)
Hypoactive upper pole (because slimmer than the midportion)
Fetal lobulation
Different number and size of the columns of Bertin

DMSA scan, static cortical scintigraphy using technetium 99m–labeled dimercaptosuccinic acid.

Indications

The main questions the clinician asks are, “What is the relative function of this kidney?” and “Is there any focal or global cortical abnormality?” Within that broad context, there are specific accepted indications for a DMSA scan (Table 8-1).

Interpretation

The DMSA scan provides information on relative renal function and on functional status of the renal parenchyma. Normally, each kidney contributes between 45% and 55% of the total renal function. A kidney that contributes between 40% and 45% must be evaluated in the clinical context. For example, the contralateral kidney to a larger duplex kidney may well contribute something in the range of 41% to 43% and be perfectly normal (because the contralateral duplex is larger and therefore has more renal cortex; see Fig. 8-1).

It is very important to recognize the normal variants of a DMSA scan and to avoid interpreting them as an abnormality. This would be a major disservice to the patient, because he or she will be labeled as someone with a “scar” in his or her kidneys and therefore as a “patient” for life. The normal variants are several (Table 8-2).

A focal abnormality with preserved outline may or may not improve later on, and a follow-up scan may be advisable, especially if the DMSA study was performed relatively early after an episode of acute pyelonephritis (Fig. 8-2). A wedge-shaped focal defect is unlikely to improve on subsequent imaging, and it is likely to represent a permanent renal scar. Therefore, the timing of the DMSA evaluation after an episode of acute urinary tract infection (UTI) is crucial to determining whether a focal abnormality is permanent or may still improve. A focal defect on a DMSA scan performed at least 6 months after acute pyelonephritis is likely to be permanent. A focal abnormality detected on DMSA in the first few months after an acute UTI may or may not improve. and a follow-up DMSA scan within 1 year is recommended.

DMSA scintigraphy is a sensitive technique. It has been shown that the DMSA scan is more sensitive than intravenous urography, ultrasonography, and even color Doppler ultrasonography in the detection of both acute lesions and late sequelae.[2,3] However, DMSA scanning is not specific, so a focal abnormality on a DMSA scan could represent various pathologies (Table 8-3). This is why anatomic evaluation of the kidney with ultrasound is an essential complement to the examination.

The relationship between extension of the anatomic lesion after VUR and infection and the scintigraphic abnormality on DMSA has been studied in animal models.[2] DMSA is normal in the absence of a macroscopic anatomic

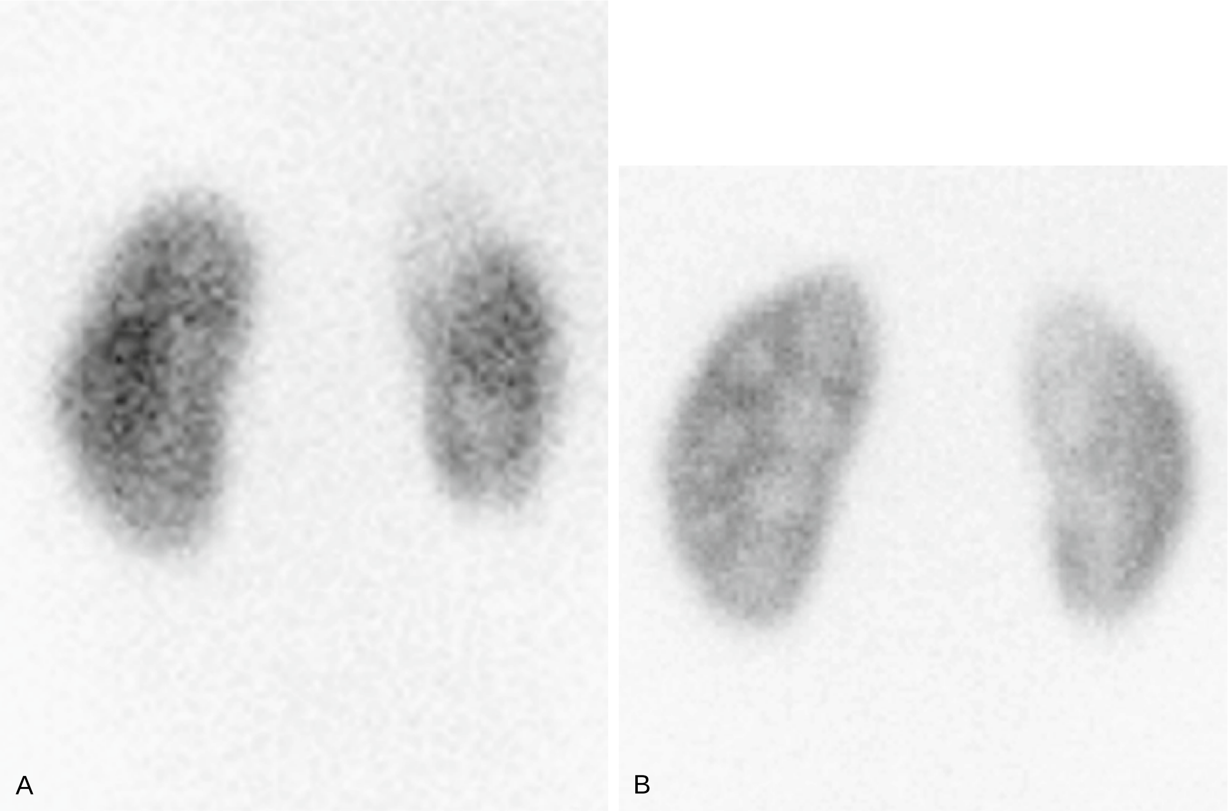


Figure 8-2 Two-year-old boy with a urinary tract infection (UTI). **A,** The first DMSA scan was performed 6 weeks after the UTI: inflammatory involvement at the right upper pole still persists. The left kidney contributes 65% to total renal function, and the right kidney 35%. **B,** The follow-up DMSA scan, performed 19 months after the UTI, shows improvement at the right upper pole. The left kidney carries 63% of total renal function, and the right kidney 37%.

Table 8-3 Differential Diagnosis of a Focal Defect on DMSA Scan

Acute renal inflammatory involvement
Renal abscess
Renal scar
Calculi
Focal cortical dysplasia
Renal cysts
Renal tumors

DMSA scan, static cortical scintigraphy using technetium 99m–labeled dimercaptosuccinic acid.

Table 8-4 The Clinically High-Risk Child with a Urinary Tract Infection

Younger than 1 year
Systemic symptoms
Unusual microorganism
Resistance to antibiotics
Late start of antibiotic treatment

lesion; a microscopic lesion, unlikely to cause a scar, is missed by the DMSA scan.

Clinical Use of the DMSA Scan

Detection of Renal Scars

Most children with UTI probably do not need imaging. Imaging in UTI should identify the susceptible child who is at a clinically higher risk of damaging his or her kidneys.

A DMSA study performed at least 6 months after a UTI can evaluate the status of the renal parenchyma and tell whether the infection has resulted in renal scarring. Extensive renal scarring is certainly associated with a higher risk of long-term complications such as chronic renal failure, hypertension, and complications related to pregnancy.[4] However, the clinical consequences of a small scar may well be negligible in terms of an increased risk of hypertension and chronic renal failure.[5] What level of functioning renal tissue (and what level of GFR) represents a cutoff point below which the risk of hypertension and chronic renal failure is higher is not known at present.

DMSA imaging to detect renal scars is indicated, together with ultrasound, in the clinically high-risk group. This group comprises patients younger than 1 year of age who present with systemic symptoms, may have an unusual microorganism in their urine, show resistance to antibiotic treatment, or perhaps have started treatment with antibiotics late (Table 8-4). The ultrasound study can show whether there is an

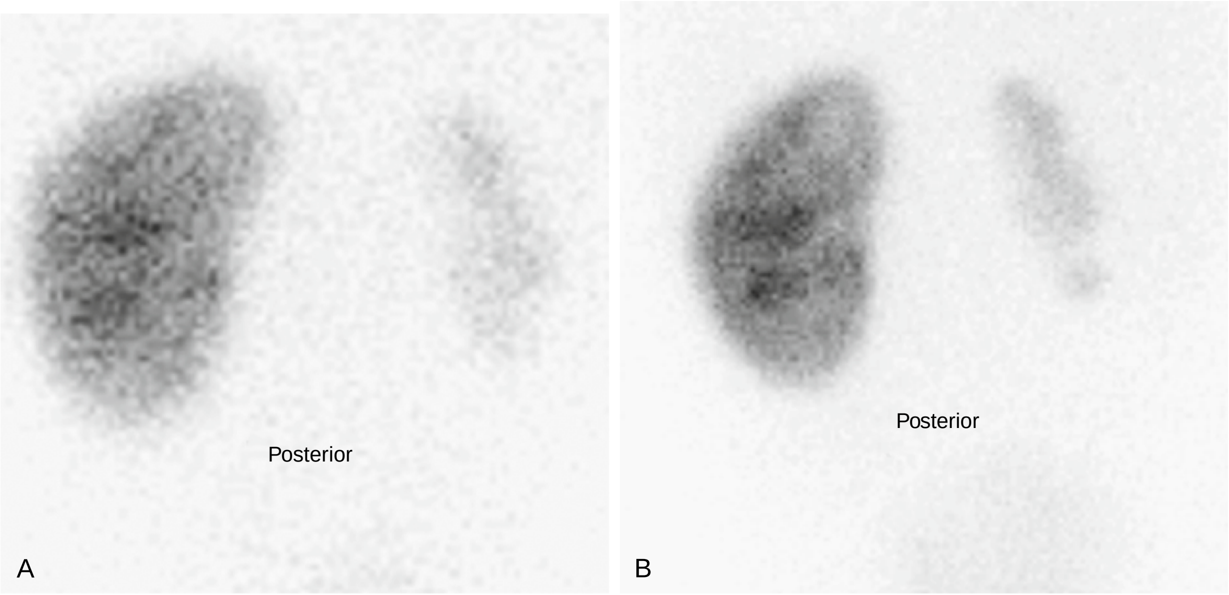


Figure 8-3 **A,** In a DMSA scan performed shortly after an acute pyelonephritis in a 6-week-old male infant, the right kidney shows global and severe reduction of isotope uptake with focal defects. **B,** The follow-up DMSA performed 13 months after the pyelonephritis shows no change. These findings are compatible with scarring involving the whole of the right kidney.

anatomic abnormality that requires surgery; the DMSA scan shows the functional status of the renal parenchyma after the infection, with the aim of predicting whether the child will be at risk for development of medical complications in the future. Some reports do not advocate the use of DMSA in this context.[6] The ability of the DMSA to predict future risk in terms of hypertension and chronic renal failure is still to be demonstrated.

DMSA in the Acute Phase of a Urinary Tract Infection

A number of clinicians and imaging specialists around the world recommend the use of DMSA scanning during an acute pyelonephritis (within 7 days from the onset of symptoms) (Fig. 8-3). The rationale is as follows: clinical symptoms of an acute pyelonephritis (fever, septic signs, loin pain, raised C-reactive protein, leukocytosis) are often nonspecific, the urine culture can be falsely negative,[7] and a DMSA scan done acutely will help clarify the diagnosis. Several papers have shown that the DMSA scan is positive in 50% to 78% cases of clinical acute pyelonephritis.[8-14] Therefore, an acute DMSA scan would help diagnose acute pyelonephritis. Moreover, if a DMSA scan is negative during the acute phase of the infection, the chance of renal scars in the future, after that infection, is zero.[15] However, critics of the use of DMSA acutely during infection say that it would not change management, because all infections are treated in the same way.

Biggi and colleagues[15] found that patients with massive renal inflammatory involvement during acute pyelonephritis had higher chance of having renal scars at follow-up DMSA. This begs the question of whether such children need to be treated more aggressively or for a longer period of time. A properly designed, randomized study could answer the question. If this were the case, a DMSA study done acutely during the pyelonephritis could be pivotal in making treatment decisions.

The relationship between reflux and renal scars is a complex one. According to a recent meta-analysis comparing the presence of renal scars to the presence of reflux on micturating cystography (MCUG), reflux is often found with normal kidneys, whereas a significant number of scarred kidneys show no reflux.[16] This suggests that patients with reflux are likely to be a heterogeneous group, some of them sustaining renal damage and others not. Reflux per se is therefore unlikely to be a good predictor of renal damage, and the use of a cystogram in every patient with UTI has been questioned. Low-grade reflux (grades I and II) is associated with a low risk of renal scarring. High-grade reflux (grade IV and occasionally grade V) has been shown to be a significant risk factor for renal scarring, according to the International Reflux Study.[17] Another recent study showed that the higher the grade of reflux, the higher the number and severity of renal scars.[18]

RADIONUCLIDE DYNAMIC RENOGRAPHY

Guidelines

A lot of effort has been put into standardizing the acquisition, processing, and interpretation of radionuclide dynamic renography scans, and a number of official documents have been produced. The "well-tempered" diuretic renogram paper[19] was mainly focused on hydronephrosis. The 1999 consensus conference[20] was an effort to standardize the estimate of the split function. The European Association of Nuclear Medicine (EANM)[21] and Society of Nuclear Medicine (SNM)[22] guidelines cover all aspects of the dynamic renal study.

Tracers

Tc^{99m}-DTPA has been used for a long time in dynamic renography. It is a small molecule that diffuses within both the intravascular and the extravascular spaces. It is filtered by the glomeruli. The extraction fraction is approximately 20%. Tc^{99m}-DTPA gives a significant background activity due to the small size of the molecule and the relatively low extraction fraction; this makes the tracer unsuitable in cases of chronic renal failure or in newborn babies with renal immaturity. Tc^{99m}-MAG3 (mercaptoacetyltriglycine) is a better tracer, is strongly protein bound, and therefore is mainly intravascular. The extraction fraction is approximately 50%. The tracer is mainly secreted by the renal proximal tubules, with a small fraction being filtered by the glomeruli. Tc^{99m}-MAG3 preparation and storage is more complex, and the tracer is more expensive than DTPA.

Iodine 123 (^{123}I)–labeled hippuran is another good-quality tracer that is mainly secreted by the renal tubules. Labeling with ^{123}I makes it an expensive tracer, and it is not always readily available. Technetium 99m–labeled ethylene-dicysteine (Tc^{99m}-EC) is another high-quality tracer with high renal extraction, but it also is not readily available.

It has been shown that, in most nonacute conditions, the glomerular and tubular functions are virtually identical in providing the renal relative function.[23] However, in the early hours of an acute total obstruction, glomerular filtration is more severely depressed than tubular function.[24]

Parameters That May Affect the Split Function

Relative renal function is an important parameter provided by radionuclide dynamic renography. This parameter depends on a number of variables. As important decisions are made on the relative renal function of each kidney, it is essential that its evaluation follow a rigorously standardized protocol. The relative renal function is estimated at a time when the tracer has reached the kidney but has not yet been excreted into the collecting system. In fact, activity pooling within the calyces or pelvis would raise the number of counts acquired from that kidney because of a contribution of counts not from the parenchyma but from the collecting system; the relative renal function from that side would therefore be artificially raised.

The background corrected tracer uptake of between 1 and 2 minutes is accepted as representing the split function (integral method).[20] The Rutland-Patlak plot[25] is meant to remove the vascular part of the background that is not completely corrected by subtracting the perirenal activity. This correction is particularly useful with tracers that have low overall extraction, such as DTPA, or in cases of low overall renal function.

Evaluation of the split function can detect differences in relative renal function between the two kidneys but cannot show a global difference in GFR when the two kidneys are equally affected or when there is a single kidney. In such cases, calculation of the single kidney glomerular filtration rate (SKGFR) is recommended. This can be estimated by calculating the GFR with a filtered molecule (e.g., chromium 51–labeled ethylenediamine tetra-acetic acid [EDTA]) and at the same time the relative renal function with a radionuclide such as Tc^{99m}-DMSA.

Diuretic Renography

Frusemide stimulation, by inducing a high-flow diuresis, has long been used during dynamic renography in the attempt to separate urinary stasis within a capacious renal collecting system from resistance to urine outflow.

Protocols of Frusemide Administration

Various protocols are currently used. Frusemide can be administered when the injected tracer has already reached the renal collecting system ("F+20"). The advantage of this protocol is that the dynamic renography before frusemide administration shows what the drainage is like in that particular patient in a situation of physiologic diuresis. If there is significant urinary stasis within the renal pelvis, then frusemide given at 20 minutes induces a high-flow diuresis, which could cause a wash-out of activity from the renal pelvis, thus distinguishing between urinary stasis and resistance to outflow.

In practice, infants with a significantly dilated renal pelvis diagnosed antenatally and a still immature renal parenchyma often show very slow drainage in the absence of a challenge with frusemide, with stasis in the renal pelvis. For this reason, many groups have turned to a different protocol, with an early administration of frusemide, either together with the tracer ("F0") or soon afterward ("F3"). This technique has the advantage of shortening the time required for image acquisition and therefore reducing the possibility of motion artifacts. Also, it avoids two venipunctures (if a butterfly is used for injection rather than a Venflon). The consequence of this approach is the induction of high-flow diuresis in the second part of the dynamic renography; this can often result in a relatively flat or slowly descending time-activity curve. This feature does not mean that there is poor drainage (in which case there would be a rising curve); rather, it means that drainage is slow because a more capacious collecting system takes longer to drain than a smaller collecting system.

The other protocol, that of giving frusemide several minutes before tracer administration ("F–15"), has been widely adopted in adults. It can be used but is not highly favored in pediatrics, because it can induce urgency to void while the acquisition is still in progress, resulting in a higher risk of an incomplete examination. Other groups favor a flexible approach in the administration of frusemide (the "F" frusemide protocol—F for *flexible*). They advocate frusemide administration at the time when persistent significant stasis within the collecting system is observed during dynamic renography.

Table 8-5 Evaluation of Drainage

Drainage depends on the following factors:
Hydration status
Volume of the renal pelvis
Function of the kidney
Position of the patient (supine versus upright)
Status of the bladder (empty, full, or partially full)

Evaluation of Drainage

Drainage of a kidney depends on the hydration status, the function of that kidney, the volume of the pelvis, the posture of the patient (effect of gravity), and the status of the bladder. Several parameters influence drainage. Methods of evaluating drainage that are based only on the half-life ($t_{½}$) of tracer washout from the pelvis are inaccurate, because they do not take into account such factors as renal function, pelvic volume, and bladder status (Table 8-5).

HYDRATION

A good hydration status is important. Ingestion of 7 mL/kg fluids (water or fruit juice) 30 to 60 minutes before tracer injection is normally sufficient. The SNM guidelines, acknowledging that oral hydration may be sufficient in some cases,

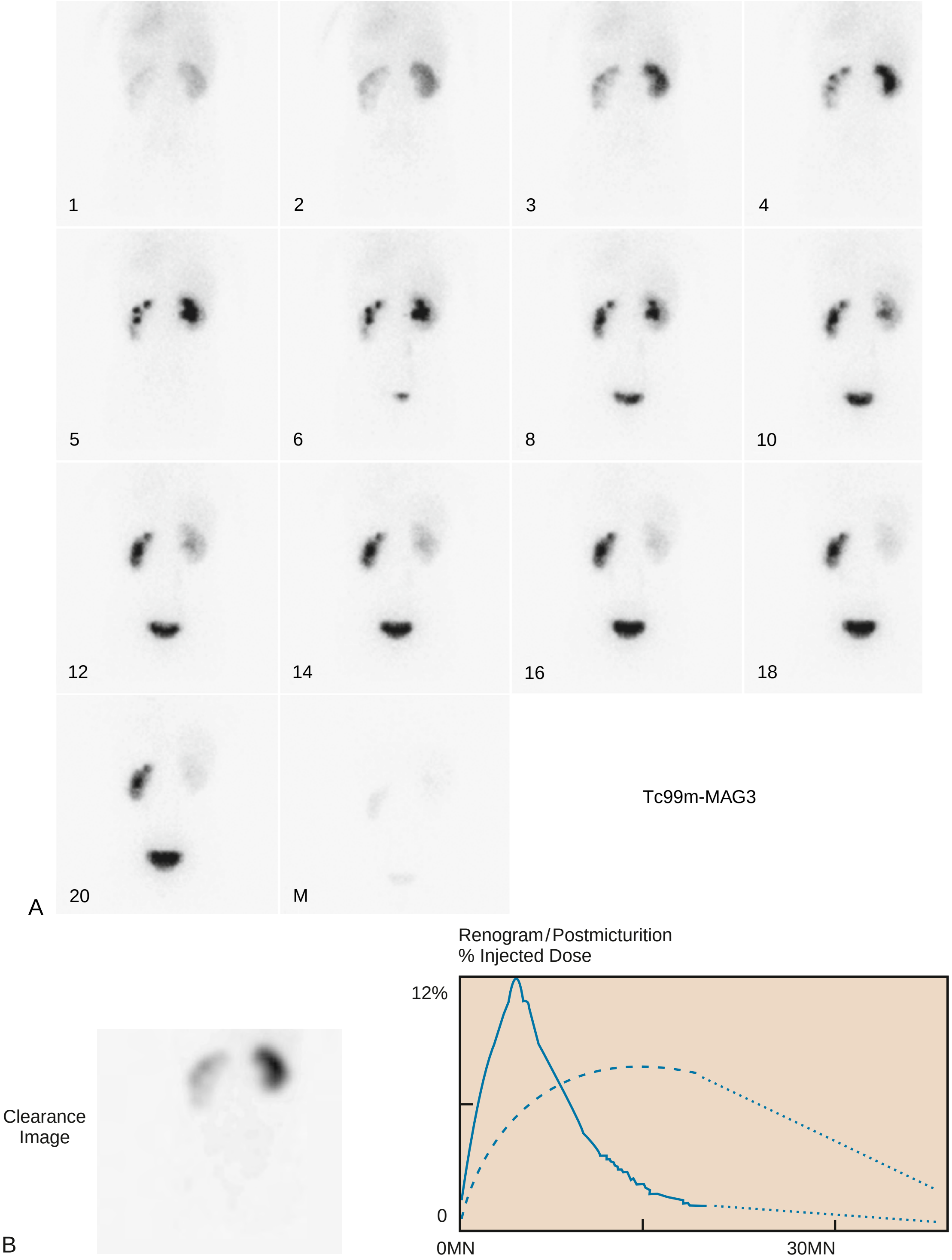
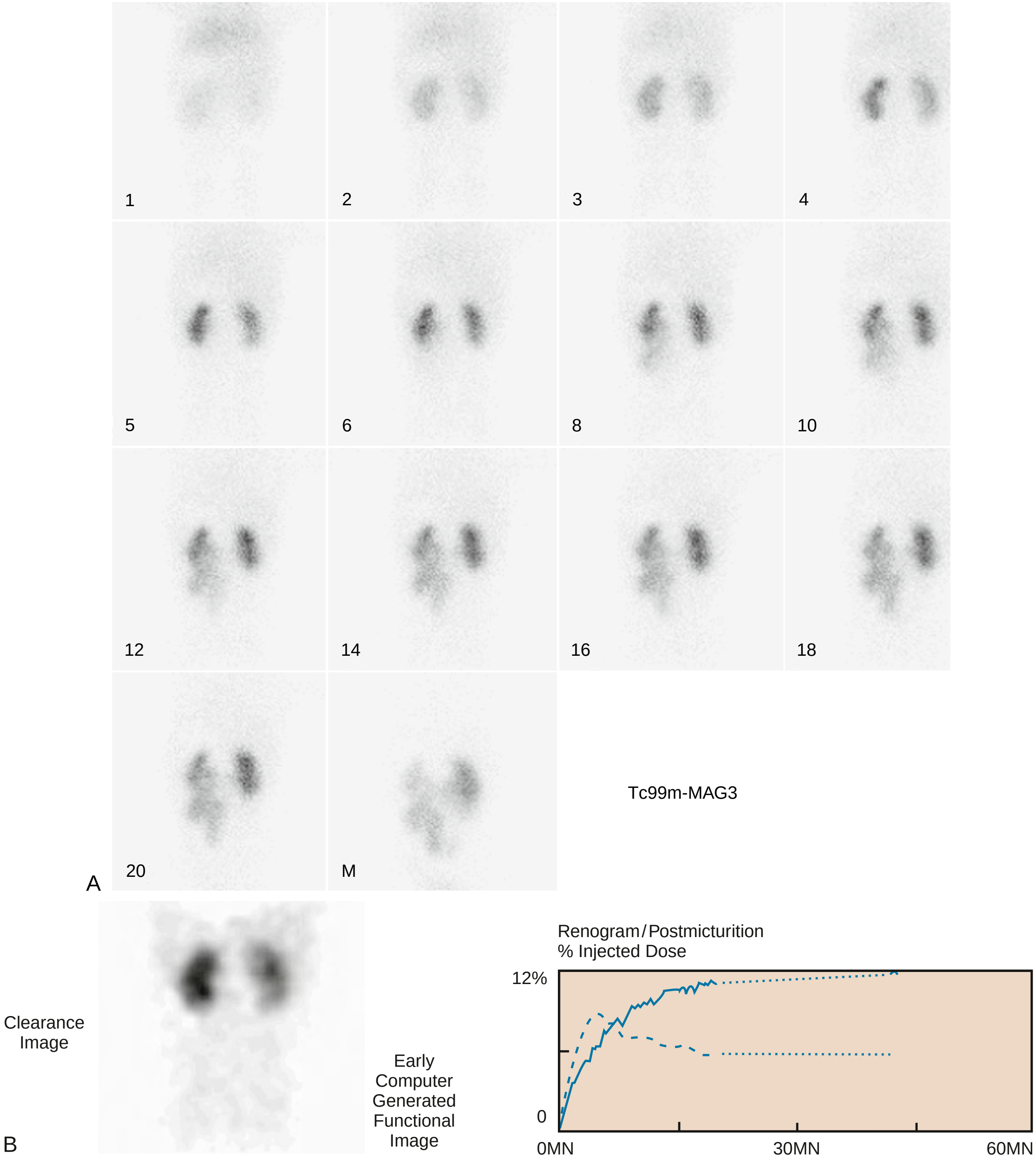


Figure 8-4 **A,** A diuretic technetium 99m–mercaptoacetyltriglycine (^{99m}Tc-MAG3) renogram in a 14-year-old boy in follow-up after a left pyeloplasty for pelviureteral junction obstruction shows stasis in the left collecting system while the child lies supine on the camera face. After a change of posture and micturition (image M), there is almost complete drainage from the left renal pelvis. The left kidney contributes 30% to total renal function, and the right kidney 70%. This case stresses the importance of the postmicturition view to distinguish urinary stasis from obstruction. **B,** Functional, or clearance, image, showing a less functional left kidney and a normally functioning right kidney. Time activity curves for the right kidney (*continuous line*) and for the left kidney (*dotted line*) are shown. Both curves are extrapolated to the postmicturition view (acquired at approximately 40 minutes after the start). The postmicturition view has been acquired in the same fashion as the dynamic renography and is therefore comparable to the dynamic study.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Early Computer Generated Functional Image
Renogram/Postmicturition
% Injected Dose
12%
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30MN
60MN

Figure 8-5 **A,** A diuretic MAG3 scan in a 7-month-old girl shows stasis within a dilated left ureter (12 to 14 mm dilatation). The image obtained after postural change (image M) does not show significant change: these findings are compatible with a dysfunctional left vesicoureteric junction and a left hydroureteronephrosis. The child had a JJ stent placed. **B,** Clearance, or functional, image, showing a well functioning left kidney and a slightly less functional right kidney. The time-activity curves show urinary stasis in the renal pelvis and upper ureter bilaterally, even following change of posture and micturition.

recommend slow intravenous hydration starting 30 minutes before tracer injection and continuing throughout the dynamic renography.[22] In Europe, this practice is not widely followed; oral hydration, both at home and in the nuclear medicine unit in the time available after application of anesthetic cream, is recommended.

Effect of Pelvic Volume

A large pelvis takes longer to drain than a small pelvis; this does not mean that the pelvis is obstructed, but simply that there is more urine in a large pelvis, and therefore a large pelvis will take longer to clear. Also, when isotope-tagged tracer reaches

Table 8-6 Causes of Renal Pelvis Dilatation

Vesicoureteric reflux
Hydroureteronephrosis
Posterior urethral valves
Congenitally dilated nonobstructed renal pelvis
Obstructed renal pelvis

a large pelvis, it will dilute with a larger amount of nonradioactive urine that pools in that pelvis, and each drop of urine leaving the pelvis will contain less isotope; therefore, isotope will leave a large pelvis more slowly.

EFFECT OF RENAL FUNCTION

A kidney with poor function takes up less isotope than a kidney with good function and therefore it takes longer for the collecting system to fill with isotope. One may therefore have the impression that the kidney shows an abnormally slow drainage, whereas in fact the drainage is appropriate in relation to the poor function of the kidney. With a very poorly functioning kidney, drainage is virtually impossible to evaluate with radionuclides.

EFFECT OF GRAVITY

The dynamic renal study in a child is normally acquired with the child lying on the camera couch; therefore, the study reflects drainage in the supine position. However, this is not the physiologic position of a person during most of the day. An image taken after some time in the upright position is necessary to assess drainage aided by the effect of gravity. This image must be comparable to the rest of the study. It is most valuable in distinguishing urinary stasis in the supine position from resistance to urinary outflow and holdup at the pelviureteral junction (PUJ) or at the vesicoureteric junction (VUJ) (Figs. 8-4 and 8-5).

EFFECT OF BLADDER STATUS

Drainage from the renal pelvis and ureter is also affected by the status of the bladder. If the bladder is full or partially full at the end of the dynamic renography (as one would expect with a normal hydration status and a lot of isotope being passed into the bladder from the renal parenchyma), there will be higher pressure in the bladder than when it is empty, and this will slow the drainage from the upper tracts. Therefore, it is essential to obtain a postmicturition view with an empty bladder at the end of the dynamic renography. Many groups, especially in the United States, place a catheter in the bladder at the beginning of the dynamic renography to make absolutely sure that the bladder is empty during the study (i.e., that drainage from the upper tracts is not slowed by an incompletely empty bladder). This approach is particularly useful in the evaluation of a possible holdup at the PUJ or at the VUJ, because a partially full bladder may cause persisting activity within the pelvis or ureter due to increased pressure in the bladder, making the assessment of a PUJ or VUJ difficult.

QUANTIFICATION OF DRAINAGE

An algorithm to evaluate drainage should take into account the relative renal function. The pelvic excretion efficiency (PEE) measures the percentage of activity that has left the kidney in relation to the activity that has been taken up by that kidney. A kidney with unimpeded drainage will show a PEE of more than 80%. The advantage of this method is the ability to take into account the relative function of the kidney; the disadvantage is that it does not take into account the volume of the pelvis. Another method in use is the "normalized residual activity" (NORA), which is a ratio between the activity at a given time during the acquisition and the activity in the kidney at the time when the differential function is calculated (usually, the number of counts from minute 1 to minute 2). When both parameters are applied, they show a relatively good correlation.[26]

The Definition of Obstruction

In pediatrics, a dilated renal pelvis observed on ultrasonography does not necessarily mean an obstructed pelvis. A dilated renal pelvis can be caused by VUR, hydroureteronephrosis, posterior urethral valves, a congenitally dilated renal pelvis with no resistance to urine outflow through the PUJ, or PUJ stenosis with resistance to urinary outflow and consequent obstruction (Table 8-6). In most patients who have a dilated renal pelvis (in hydroureteronephrosis the ureter is also dilated), there is no resistance to urinary outflow; the pelvis takes longer to empty simply because it is bigger. If the patient is a neonate or an infant (especially during the first 3 to 4 months of life), the renal parenchyma is immature; the uptake in the cortex is lower than in a fully developed kidney, and the transit of tracer through the renal tubules is slower. As a result, the tracer takes longer to get to the renal pelvis and is more diluted in the nonradioactive urine; consequently, it leaves the renal pelvis more slowly.

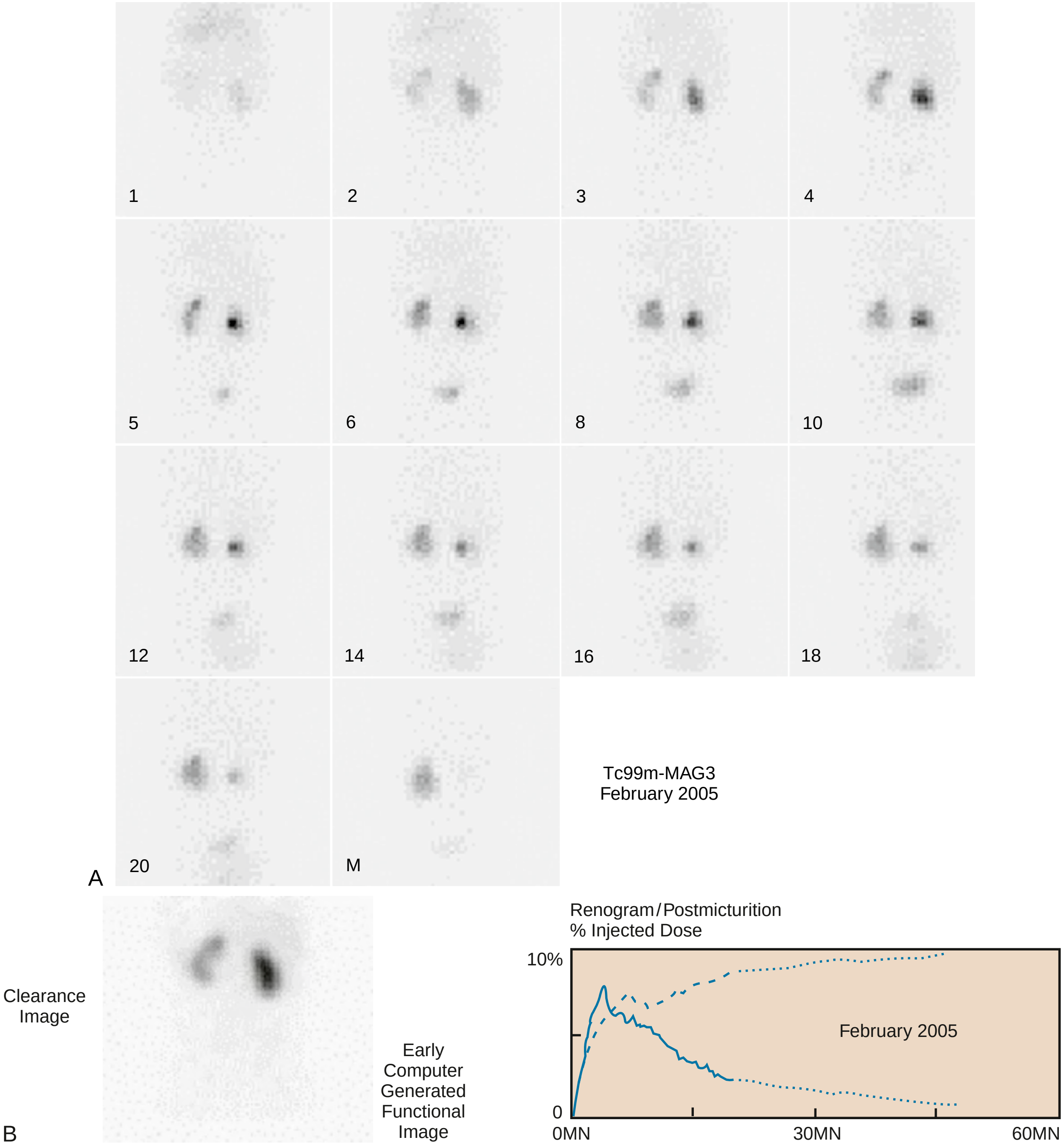
The degree of narrowing at the PUJ, at the VUJ, or at the bladder outlet can be tight or not so tight, causing a wide spectrum of conditions ranging from severe, almost complete, acute obstruction to chronic, partial obstruction. A typical example of severe obstruction may be observed in a patient with posterior urethral valves, a condition that can cause severe renal impairment due to high resistance to urinary outflow in the urethra. Most children with antenatally detected hydronephrosis have a chronic, partial PUJ obstruction that does not cause renal deterioration. Not every hydronephrosis with urinary stasis and holdup at the PUJ causes progressive renal damage; in fact, few kidneys with antenatally detected hydronephrosis show progressive renal deterioration if untreated.

Obstruction causes progressive renal damage if not treated. Therefore, the only accepted definition of obstruction in pediatrics is a retrospective one. Obstruction can be defined as "any restriction to urinary outflow which, left untreated, will lead to progressive renal deterioration."[27] Therefore, in the patient population with antenatally detected hydronephrosis, it is not possible to diagnose obstruction on a single dynamic radionuclide renogram. At least two isotope scans in succession are necessary, and renal obstruction will be diagnosed on the second scan if there has been a significant fall in the relative function of that kidney, with either a new focal defect or a global reduction of uptake (Fig. 8-6). If the relative function has not changed significantly—in absence of any symptoms, although these children are usually asymptomatic—this means that the renal parenchyma and the excretory system are in equilibrium (i.e., the collecting system excretes the amount of urine produced at that particular level of renal function). Drainage can be very slow, with significant stasis at the PUJ, but this does not mean that the kidney is obstructed (Fig. 8-7). In more than 50% of children with antenatally detected hydronephrosis who were treated conservatively, the drainage was slow.[28]

Drainage that has been slow for a long time can eventually improve (see Fig. 8-7). Hydronephrosis is not necessarily associated with renal damage. Hydronephrosis can be actually a protective mechanism whereby the kidney defends itself from an increasing pressure within the renal pelvis as a result of narrowing of the infundibulum at the PUJ.[27]

Antenatally Diagnosed Hydronephrosis: Conservative Versus Surgical Approach

With the advent of antenatal ultrasonography in the early 1980s, a completely new patient population came under medical attention: patients with congenital hydronephrosis. Once diagnosed, these patients were followed up postnatally, in spite of being asymptomatic, because of the hydronephrosis.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Early Computer Generated Functional Image
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Renogram/Postmicturition
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Figure 8-6 Obstruction is a condition of urinary outflow which, if left untreated, will lead to increase in dilatation of the renal pelvis and deterioration of renal function. This case shows increasing hydronephrosis of the left kidney in a 3-year-old girl (**A** and **B**). At the time of the first isotope scan (February 2005), the left renal pelvis measured 8 mm, and the left kidney contributed 45% to total renal function. The time-activity curves show good drainage from the right kidney and progressive tracer accumulation in the left kidney, even after change of posture and micturition (the postmicturition view was acquired approximately 47 minutes after the start of the dynamic renography).

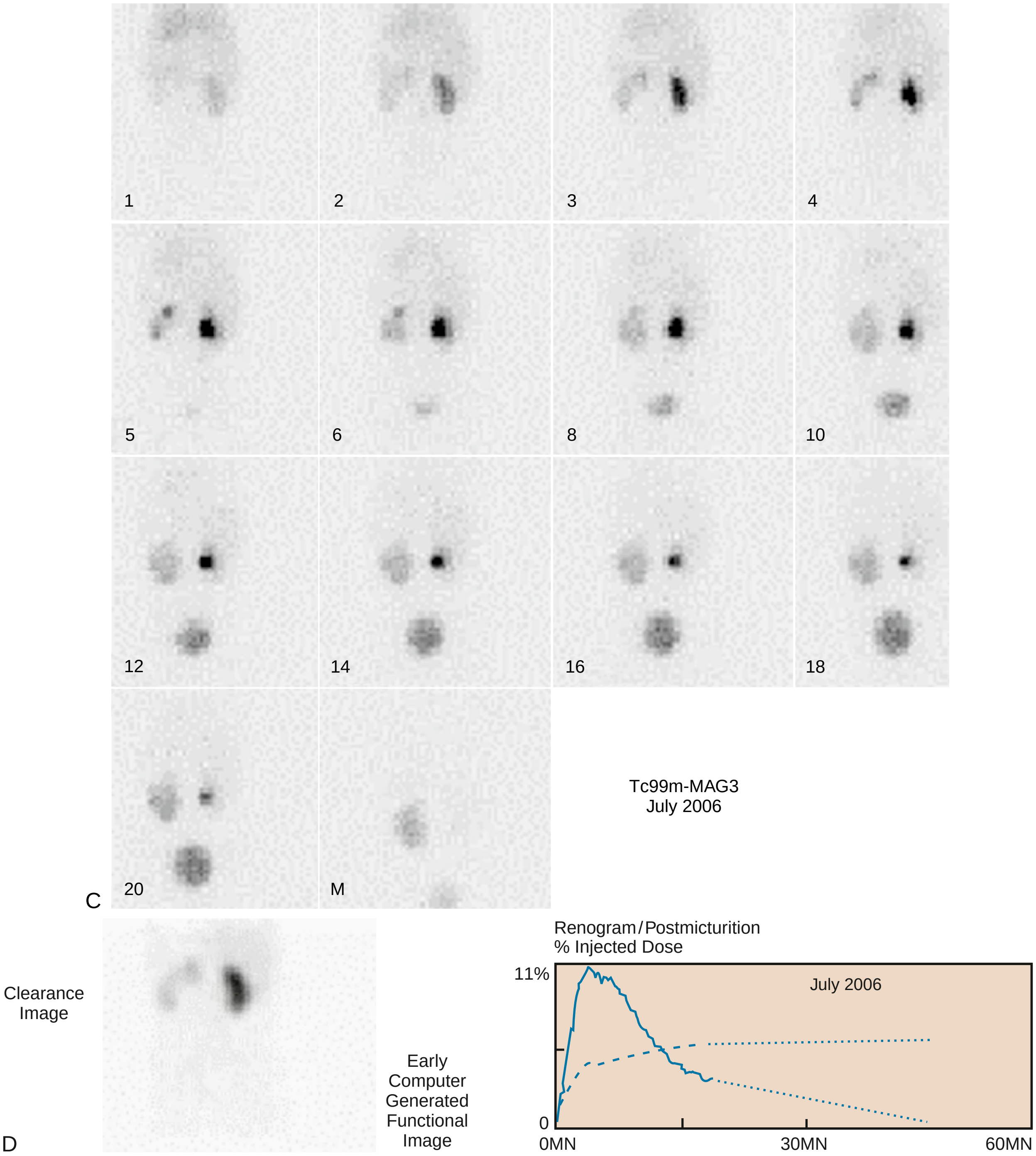
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Figure 8-6, cont'd, **C** and **D,** On subsequent ultrasound scans, the size of the left renal pelvis progressively increased to 41 mm in July 2006, when a repeat MAG3 scan showed a significant deterioration of the function of the left kidney, to 24%. The left kidney was obstructed, and this caused deterioration of left renal function together with an increase in pelvic size. The clearance image shows a poorly functioning left kidney and a well functioning right kidney. The time-activity curve of the left kidney (*dotted line*) clearly shows impaired drainage, even following change of posture and micturition, while the right kidney drains well.

Before the introduction of antenatal ultrasonography, the vast majority of this patient population went undetected. Some of them developed renal obstruction, calculi, or infections later on and presented to medical attention; they were all treated surgically. Early after the introduction of antenatal ultrasound, the same surgical approach was applied to every patient with antenatally detected hydronephrosis. Only later was it thought that perhaps not all of these patients needed surgery. The conservative approach of watchful waiting began to be adopted by several groups. In some groups, the percentage of patients with antenatal hydronephrosis who were referred to surgery fell to about 20% or 25%.

Nowadays, most patients with antenatally detected hydronephrosis are treated conservatively. Some patients are treated surgically. The criteria for surgery are still variable among different surgical units. Many surgeons decide whether to perform a pyeloplasty based on the relative function of the hydronephrotic kidney on radionuclide renography and the size of the renal pelvis on ultrasonography. Kidneys with reduced function (<40% of total renal function) and with a very dilated renal pelvis (>30 mm) are considered for surgery.

It is still relatively early to tell which strategy is best in the long term for children with antenatally detected hydronephrosis. The conservative approach has the advantage of limiting possible complications related to surgery to those patients who certainly need surgery. A disadvantage is the possible loss of function of a kidney that has been monitored with ultrasound and in which the relative function has decreased. In his comprehensive review, Josephson[29,30] allocated to the watchful waiting group a cohort of 474 neonates; only 10% eventually underwent surgery because of increased renal pelvis dilatation and/or decreasing split renal function. The surgical approach has the advantage of better preservation of renal function and avoiding a long-term follow-up. The disadvantage is that surgery may be performed in children that actually do not need it.

CONGENITAL ABNORMALITIES

Duplex Kidney

An uncomplicated duplex kidney is a variation of normality. The complicated duplex may be a complete or an incomplete duplex. Both moieties may show equal function, and in such cases the duplex kidney is typically longer than normal and has divided renal function greater than 55% (Fig. 8-8). Reduced

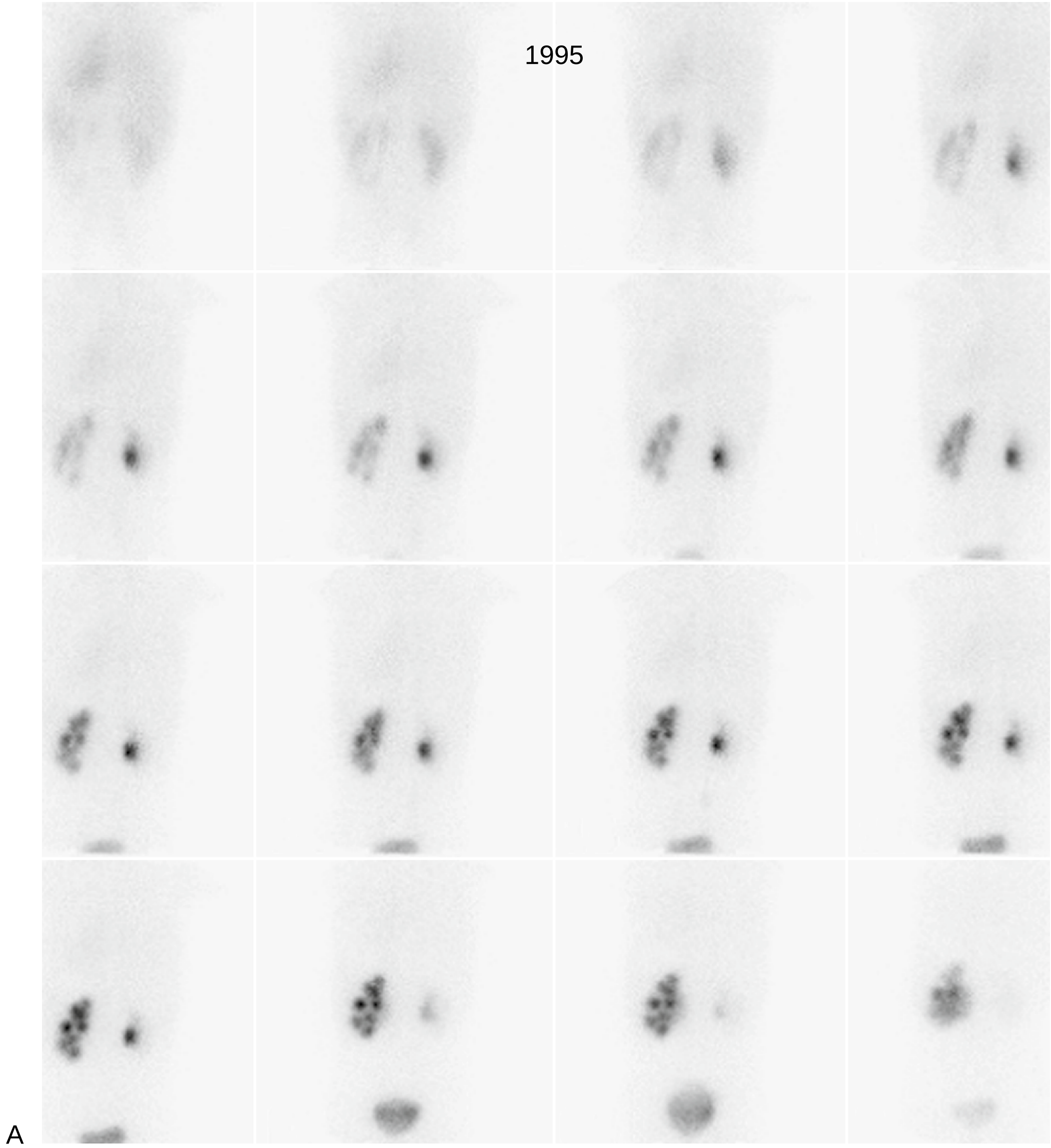

Figure 8-7 Slow drainage with urinary stasis at the pelviureteral junction does not necessarily mean obstruction. Obstruction is diagnosed if the renal pelvis increases in size on repeat ultrasonography or the relative function of that kidney falls on follow-up MAG3 scanning, or both. This case shows a 4-year-old girl with a left hydronephrosis who was monitored for 10 years: the dynamic renogram showed slow drainage from the left renal pelvis at the first MAG3 renogram in 1995 (**A**) and on the follow-up renogram in 1999 (**B**). The relative function of the left kidney was virtually unchanged and the size of the left renal pelvis was also stable.

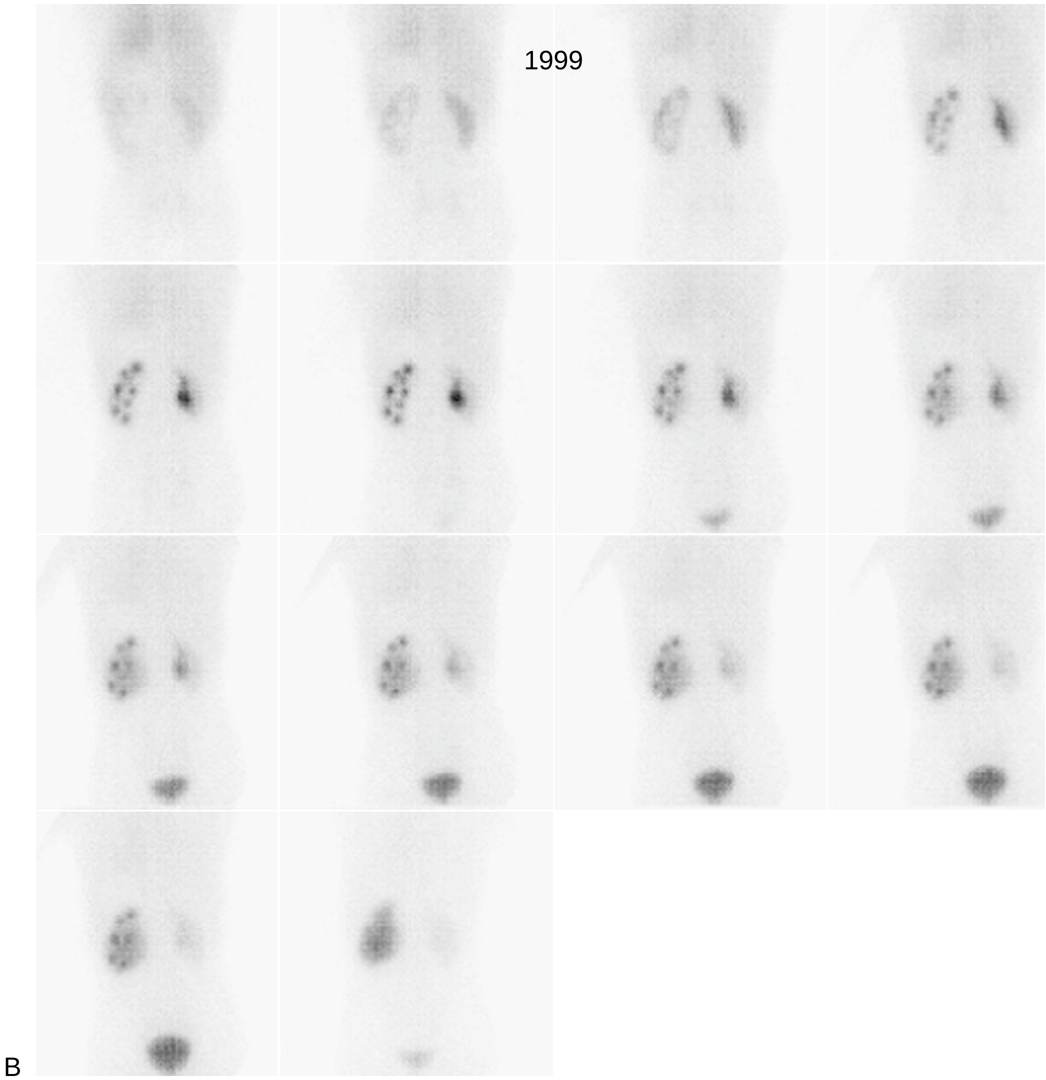

Figure 8-7, cont'd

function of the upper moiety may be a result of dysplasia (Fig. 8-9) or obstruction due to a ureterocele (Fig. 8-10), or both. The lower moiety may have reduced function in association with reflux into this moiety or because of obstruction at the PUJ level (Fig. 8-11).

Drainage—Incomplete Duplication

Drainage of the duplex kidney is by definition via two collecting systems. However, the two systems have many possible formations. In the case of incomplete duplex, the two ureters may join at any level above the bladder. Urine may reflux from one moiety down the ureter and then up into the other moiety, rather than going down into the bladder; this is known as "yo-yo" reflux. It is only on dynamic radionuclide studies that this diagnosis can be made with certainty.

Drainage—Complete Duplication

In complete duplication, the ureters draining the two moieties never join. If both ureters drain into the bladder, the ureter draining the lower moiety is prone to reflux. The ureter draining the upper moiety usually enters the bladder as a ureterocele and is frequently obstructed. The ureterocele may vary in size, from being so large that the inexperienced practitioner may mistake it for the bladder to being so collapsed that it is not recognizable even on a careful ultrasound examination. If one moiety drains outside the bladder, it is usually the upper moiety, and this ureter can terminate in the urethra or in the vagina in girls. Such ectopic drainage of the ureter is almost always associated with dysplasia of the upper moiety of the kidney.

Clinical Presentation

The child with duplex kidney may present with a number of clinical conditions:

- Asymptomatic (i.e., duplex system discovered as an incidental finding)
- Urinary tract infection
- Pain, which can be secondary to an intermittent obstruction at the PUJ level of the lower moiety or caused by yo-yo reflux with incomplete duplication

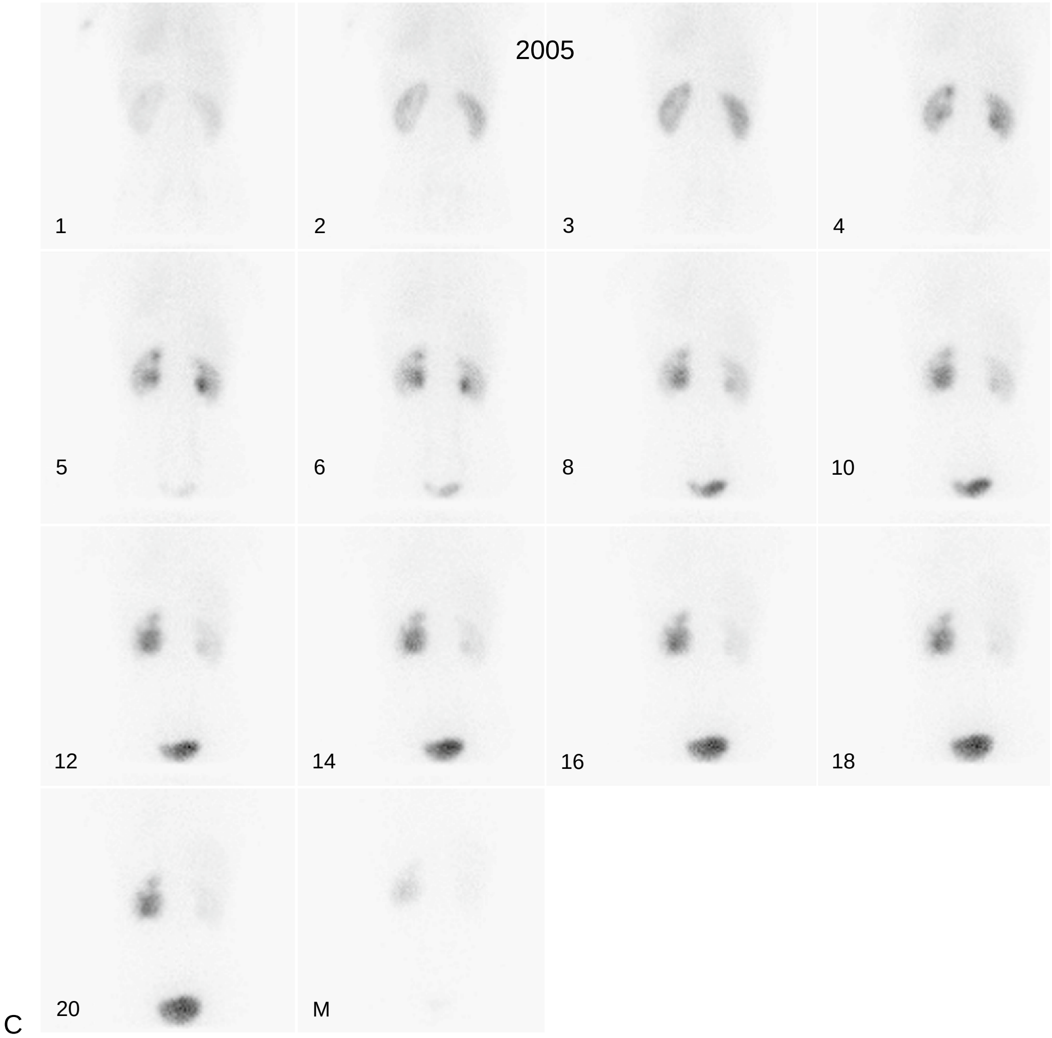

Figure 8-7, cont'd, C, The final scan, at 14 years of age, shows stasis in the left renal pelvis when the girl lies supine on the camera couch and good drainage after postural change and micturition. This girl never had any surgery, because the size of the left renal pelvis never increased significantly, and the split function of the left kidney never fell significantly. This is an example of a dilated renal pelvis coping with the amount of urine excreted without significant resistance to outflow.

- Continuous wetting in the girl who has never been dry due to an ectopic insertion of the upper moiety into the vagina
- Vaginal prolapse, which may occur when the ureterocele prolapses out of the bladder. (Prolapse of a ureterocele may also result in bladder neck obstruction and may mimic posterior urethral valves in boys.)

Imaging

One of the cardinal signs of a duplex system is a change in the axis of the lower moiety. This is best noted by the fact that the calyces of the lower moiety are medial to the upper group of calyces, giving the lower moiety of the kidney a longitudinal axis pointing to the shoulder on the same side. The appearance of a duplex kidney varies with the pathology of each moiety. ^{99m}Tc-MAG3 scanning can assess function, drainage, and reflux, especially with late images. If a moiety is nonfunctional, it will not be visualized; this is important when there is a small, severely dysplastic upper moiety. A high index of suspicion when reporting on functional imaging allows the duplex kidney to be recognized easily.

With incomplete duplication, the upper and lower moieties may be normal, or there may be reduced function of either element. With ^{99m}Tc-MAG3 scanning, the drainage from each moiety can be evaluated and evidence of yo-yo reflux can be sought.

Fusion Abnormalities

The most common fusion abnormality is that of the *horseshoe kidney* with fusion of the lower poles; this is always associated with malrotation so that the pelves and ureters pass anteriorly over the fused lower poles. The two well-recognized complications are renal pelvis dilatation (with or without obstruction) and renal calculi. The abnormal position also leaves the kidney more susceptible to injury. A ^{99m}Tc-DMSA scan with an anterior view is useful to show all functioning renal tissue, especially over the spine (Fig. 8-12).

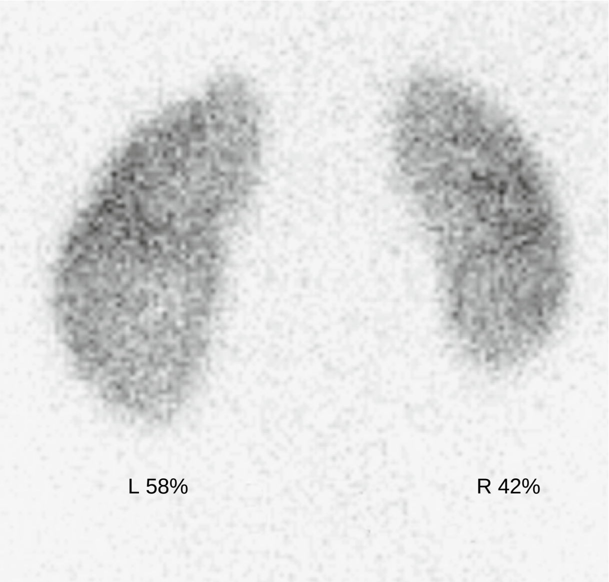

Figure 8-8 A left uncomplicated duplex kidney: there is normal uptake in both the upper and lower moieties, which function as a single unit. The left kidney is larger than the right, and therefore the mass of functioning nephrons is bigger. This is why the relative function of the left kidney is slightly higher (58%) than the accepted normal range of 55% to 45%. The right kidney is entirely normal, although it contributes only 42% to total renal function.

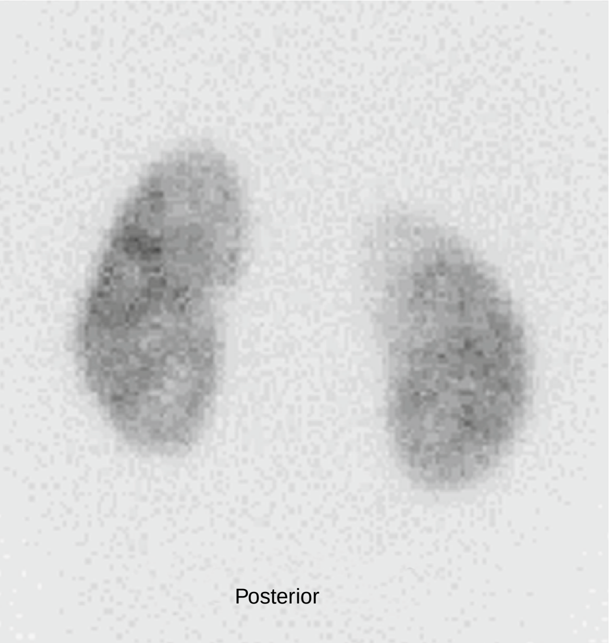

Figure 8-9 A 4-year-old girl who was constantly wet. The DMSA scan shows reduced uptake at the right upper pole, which in the clinical context is compatible with the upper moiety of a duplex kidney with reduced function. A previous ultrasound had missed this finding, which was confirmed by a second ultrasound guided by the DMSA result. The girl underwent a right upper pole heminephrectomy with resolution of her symptoms.

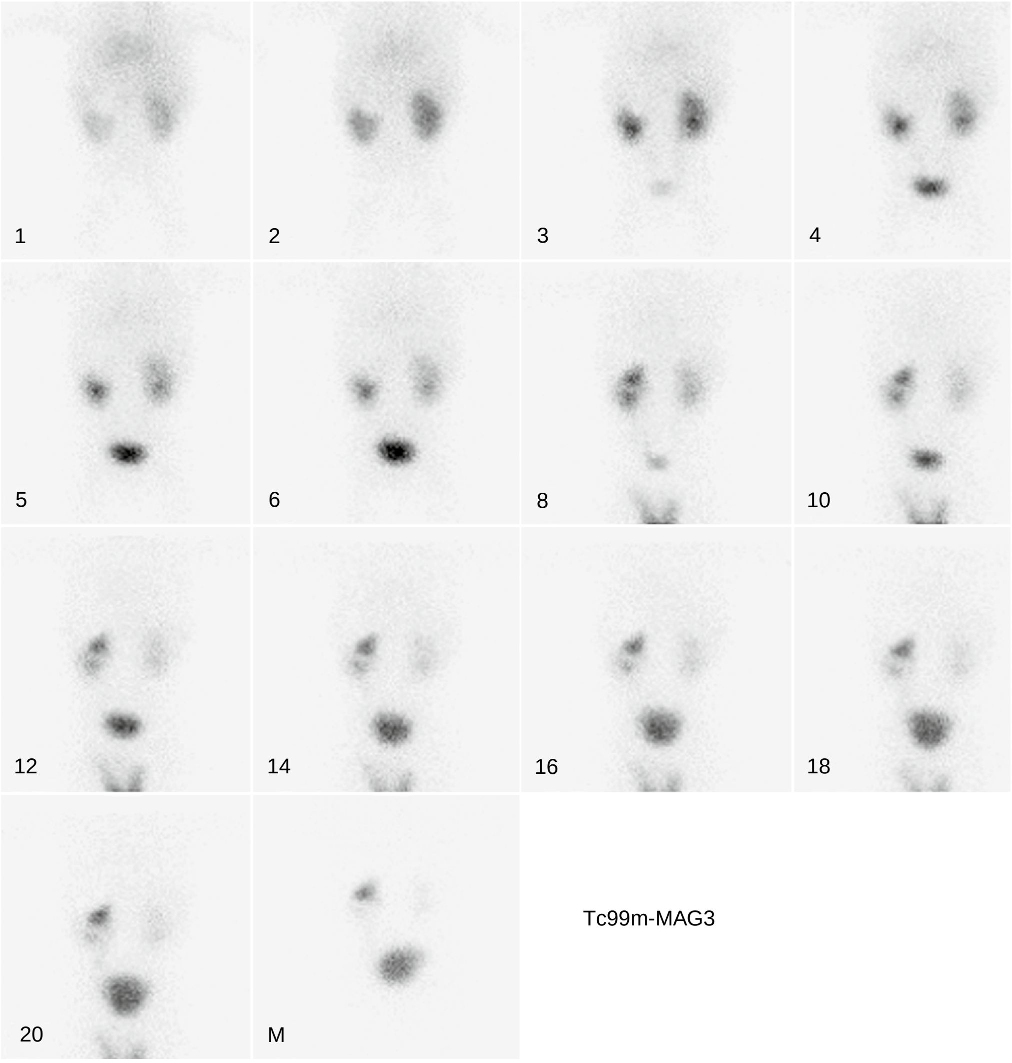

Figure 8-10 A 9-month-old boy with an antenatal diagnosis of a left duplex kidney and a ureterocele. The MAG3 study shows no uptake in the left upper moiety and good uptake in the left lower moiety. At minute 8 of the acquisition, the child voided into the diaper, and there was concomitant reflux into the left upper moiety. The child underwent a left upper pole heminephrectomy.

Crossed fused renal ectopia occurs when one kidney is displaced across the midline and fused inferiorly to the other, relatively normally positioned kidney. Both ureters enter the bladder in a normal position. The importance of this condition is that it may present as an abdominal mass or as an obstructive uropathy with a PUJ obstruction. A MAG3 renogram is required, especially if surgery is being considered for PUJ obstruction. There is an increased incidence of VUR into the crossed fused kidney, and, if further anatomic information concerning the ureter and pelves is required, an indirect radionuclide cystogram (IRC) may prove helpful (see later discussion). The ^{99m}Tc-DMSA scan may be normal or may show patchy uptake of isotope owing to the anatomic abnormality and dysplasia that may coexist to some degree.

DIRECT RADIOISOTOPE CYSTOGRAPHY

Indications

Direct radioisotope cystography (DIC) is indicated whenever renal reflux must be excluded. This group of patients mainly includes non–toilet-trained young girls with a history of UTI and non–toilet-trained boys who require follow-up cystography (having previously had an MCUG). There are no contraindications.

Method

The method is similar to that for MCUG, with instillation of ^{99m}Tc pertechnetate (20 MBq) and warm normal saline until the bladder is full, when micturition should occur. The entire procedure is carried out on top of the gamma camera linked to a computer system with a double disposable diaper on the infant. Both renal areas and the bladder are kept in the field of view (Fig. 8-13). Sedation is never required.

Clinical Evaluation

The advantages of the DIC are a high sensitivity for reflux, because the acquisition of data is continuous during bladder filling and emptying, and a very low radiation burden (0.012 mSv, which is one-fourth of the exposure with a chest radiograph). The latter feature allows repetition of the procedure

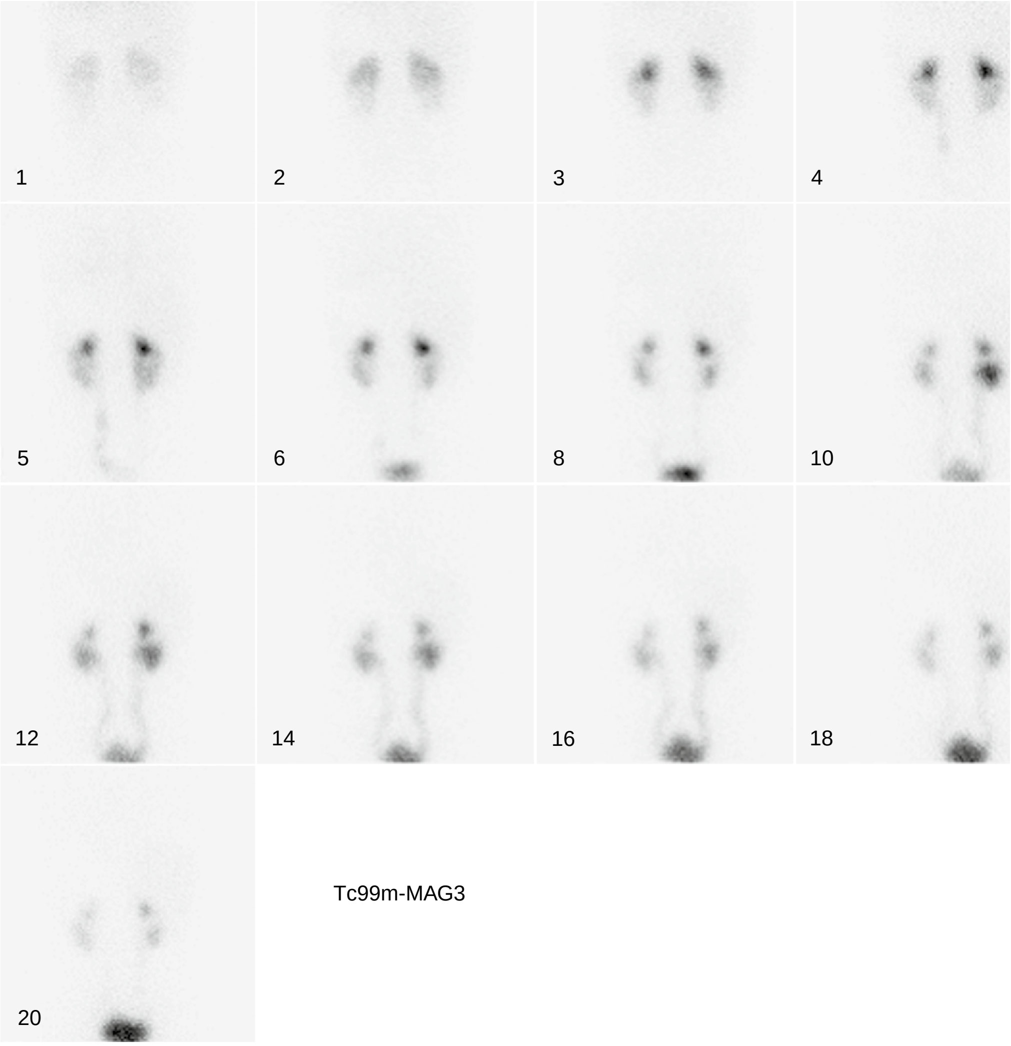

Figure 8-11 Bilateral duplex kidneys with symmetrically reduced function in the lower moiety bilaterally. The dynamic renogram also shows bilateral reflux coincident with an episode of micturition (images 10 and 12).

as often as necessary. The disadvantages are poor anatomic definition of the bladder and inability to study the anatomy of the urethra and, consequently, to exclude pathologies such as posterior urethral valves and syringocele. This is the reason why it is important, in a boy who needs cystography, to first perform a radiologic MCUG to obtain a detailed anatomic study of the urethra. Follow-up studies can be performed with a DIC until the boy is potty trained, after which IRC can be done. Girls normally do not need an MCUG, because the urethra is much shorter in girls, and urethral pathology is less relevant.

INDIRECT RADIOISOTOPE CYSTOGRAPHY

The IRC assesses renal and bladder function, does not require a bladder catheter, and detects reflux under normal voiding conditions. IRC is undertaken after the intravenous injection of ^{99m}Tc-DTPA, ^{123}I-hippuran, or, commonly, ^{99m}Tc-MAG3, which is the preferred radiopharmaceutical and has a higher extraction fraction than DTPA. Once the majority of the isotope is in the bladder, the child is asked to void in front of the gamma camera.

Indications

The IRC is indicated under the following circumstances:

- Whenever renal reflux must be excluded in the older, toilet-trained child
- Ureteric dilatation in the toilet-trained child
- In children with bladder dysfunction, including posterior urethral valves, where the entire nephrourologic system can be evaluated

Method

After a routine ^{99m}Tc-MAG3 scan, the child returns to the gamma camera, which has been turned to the vertical position, when she or he wishes to void. The child sits with the camera at his or her back; often, boys prefer to stand. Acquisition starts 30 seconds before micturition and continues for 30 seconds

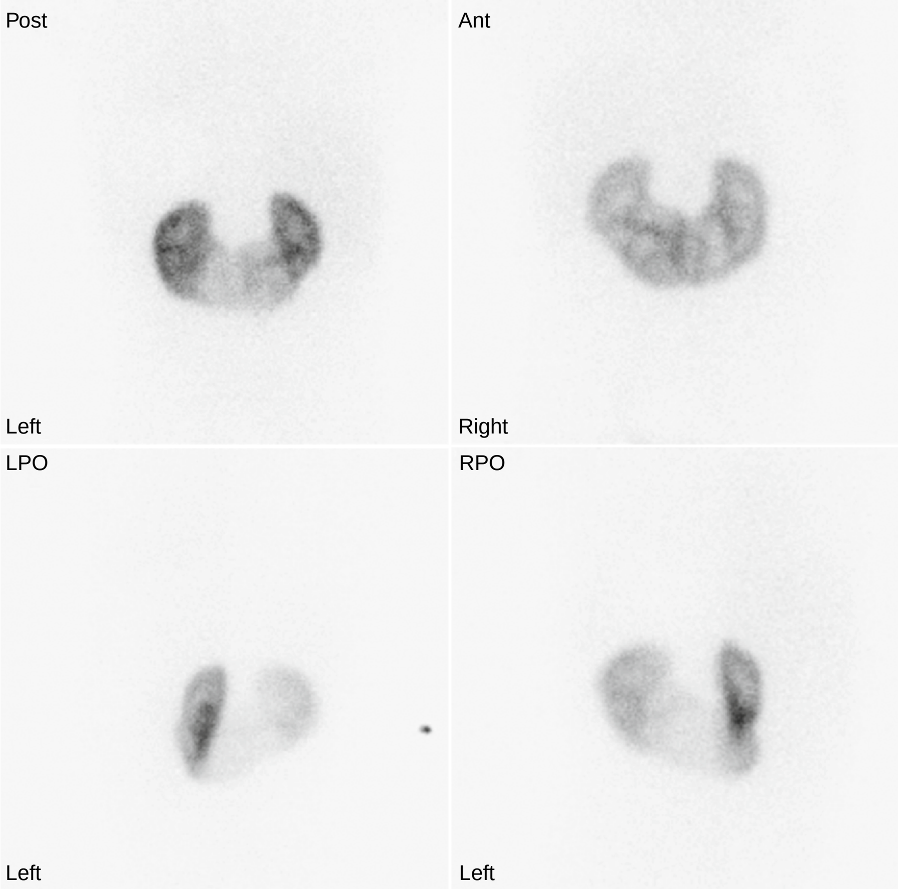

Figure 8-12 Horseshoe kidney. The DMSA scan presented in this illustration shows good uptake in each portion of the horseshoe kidney and in the isthmus as well. With ultrasound, it may be difficult to visualize the isthmus, as in this case where it was missed. (From Bajpai M. Imaging of the urinary tract in congenital anomalies. In: Bajpai M, Gearhart JP, Hjalmas K, et al., eds. *Progress in Paediatric Urology*. Vol 8. London: Penwel Publishers; 2006:138, Fig. 2b, with permission.)

after the end of micturition, with continuous data acquisition. Processing includes viewing the data in cine mode, drawing regions of interest (ROI) over the bladder and kidneys, and creating a compressed image of the entire procedure (Fig. 8-14). At the end of the cystogram, if there is persisting activity within the bladder or the collecting systems, it is our practice to undertake a second cystogram, and so on until the activity in the bladder or collecting system has been cleared. In this way, reflux may well be shown on the second or third cystogram, after a negative first cystogram, and the sensitivity of the test for reflux increases.

Clinical Evaluation

The IRC is the only completely physiologic examination that can show in vivo the pathophysiology of bladder filling (during dynamic renography) and emptying (during cystography). Although it does not grade reflux with the anatomic definition of the MCUG (grades I through V), it is possible to distinguish a mild from a moderate or a severe reflux and to roughly quantify the volume of urine refluxed.

Debate exists concerning the real usefulness of the IRC. Critics maintain that its sensitivity is significantly lower than that of the direct techniques, which involve the use of a catheter,[31] and that high-grade reflux with severe cortical damage can be observed on DIC even when the IRC is negative. Those in favor of the IRC point out that reflux can be missed by both techniques.[32] It is our experience that an IRC study with more than one cystogram performed (if there is residual activity in the bladder or collecting systems at the end of the first cystogram) can show reflux on the second or third cystogram even if the first cystogram was negative for reflux. Therefore, the sensitivity of the IRC for reflux is probably higher than what is reported in the literature. Moreover, the use of a catheter to fill the bladder creates a nonphysiologic environment for study of bladder filling and emptying. Worldwide, there is a large variability in practice: the IRC is popular in many European countries, whereas it does not enjoy much favor in the United States.

The IRC can be used to study bladder function, in particular the timing and completeness of bladder emptying, through in vivo monitoring. This helps to raise the suspicion of pathologies such as bladder instability (ineffective contractions of the detrusor) and lack of coordination of the detrusor and sphincter contraction, which result in a large residual in the bladder after voiding. A rough estimate of the residual volume of urine in the bladder is also possible.

The IRC can also be used to study drainage from the upper tracts with a full and an empty bladder and to look for a dysfunctional VUJ. Good hydration of the patient is essential.

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For complete list of references log onto www.expertconsult.com

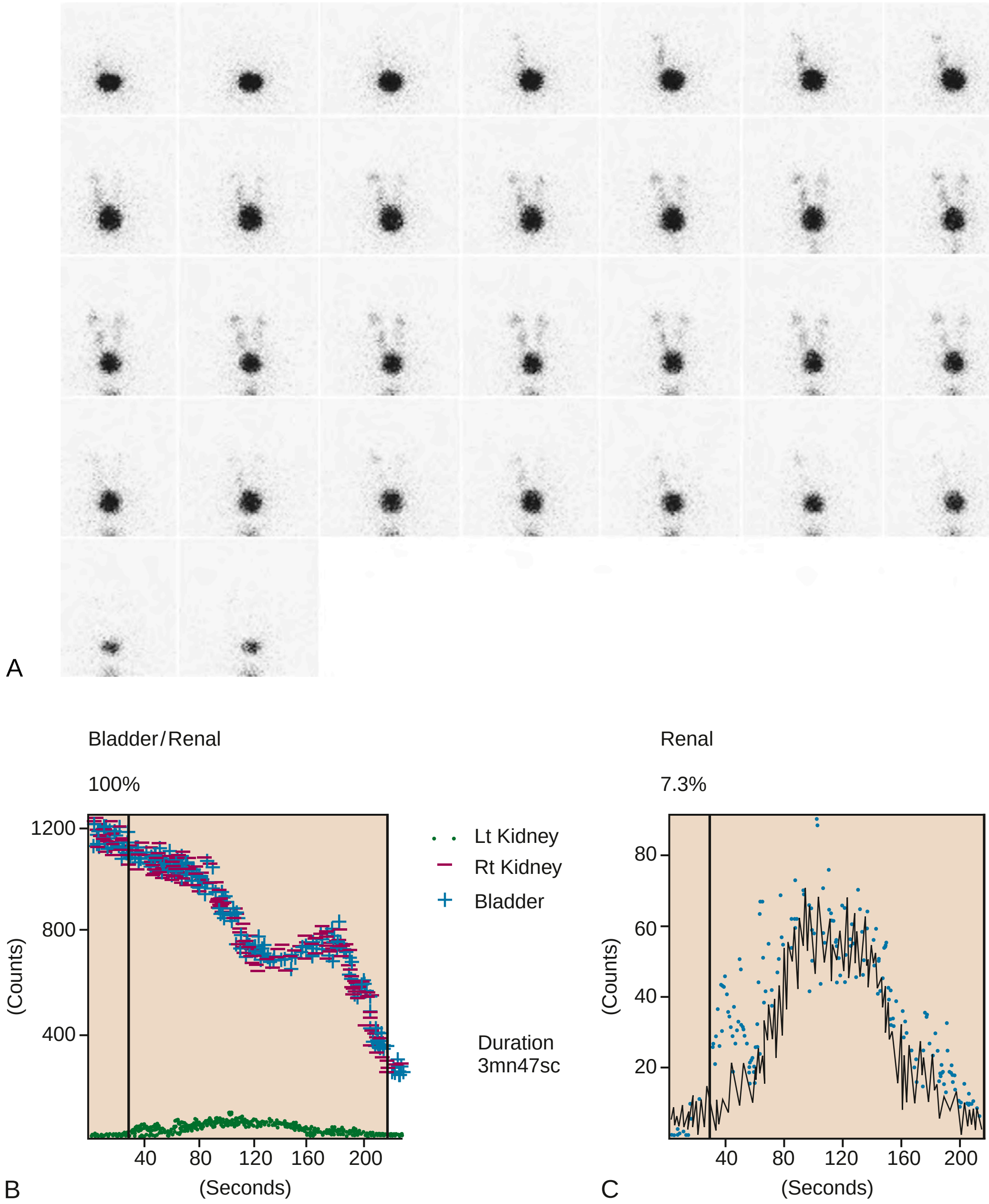
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Figure 8-13 **A,** Example of a direct isotope cystogram, showing bilateral vesicoureteric reflux. **B** and **C**, Time-activity curves describing the variation in counts within each kidney when the counts from the kidneys have been scaled to the bladder (**B**) or are considered in isolation (**C**). The curves (especially in **C**) show clear increase in counts over the two kidneys, in keeping with reflux.

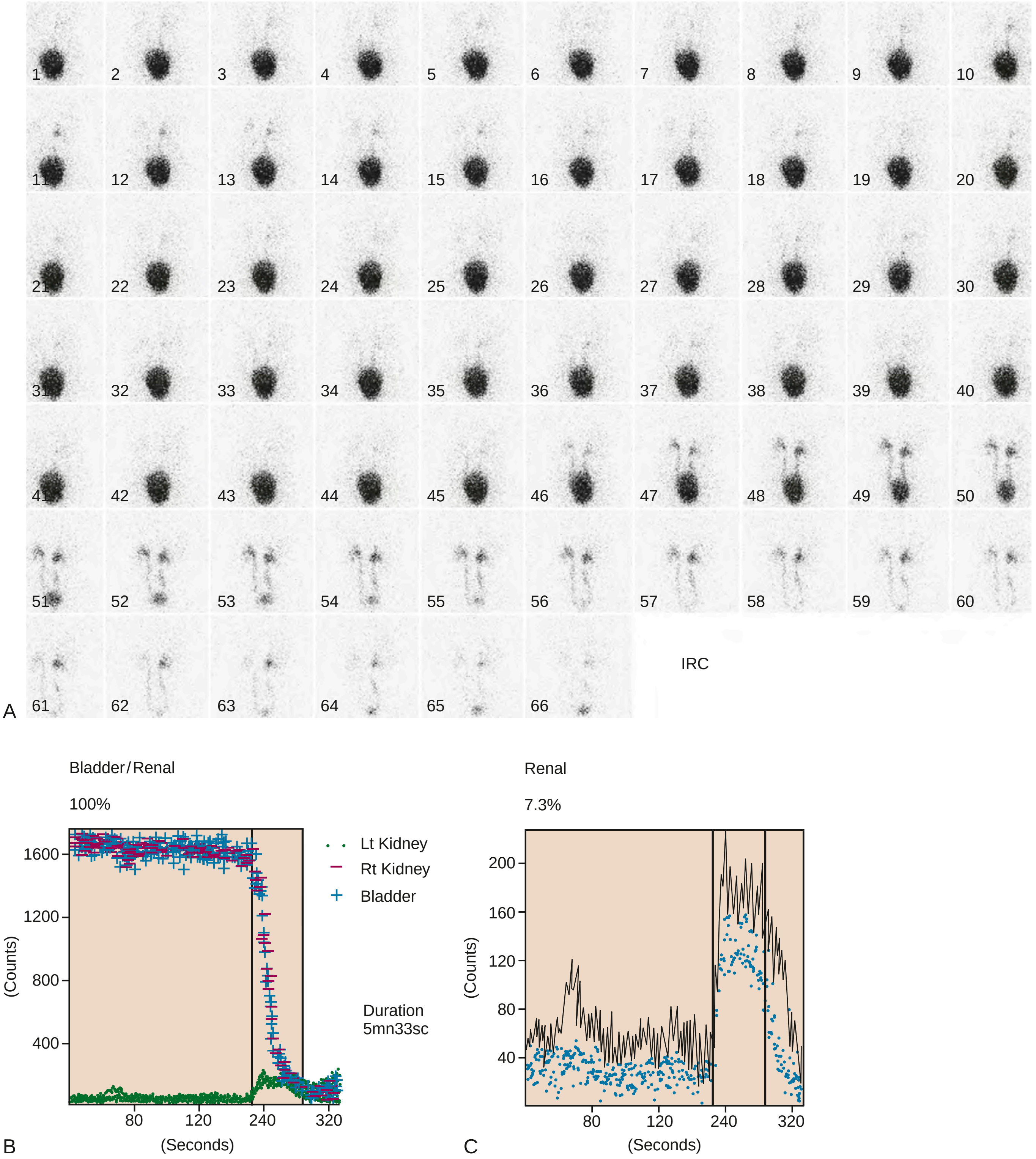
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Figure 8-14 **A,** Example of an indirect isotope cystogram in a 9-year-old girl with a history of urinary tract infection and scarred kidneys. There is bilateral reflux and complete bladder emptying. Note that there are two episodes of reflux into the right kidney during the cystogram. **B** and **C,** Time-activity curves showing the variation in counts within each kidney when the counts from the kidneys have been scaled to the bladder (**B**) or are considered in isolation (**C**). The curves (especially in **C**) show clear increase in counts over the two kidneys, in keeping with bilateral reflux.

CHAPTER 9

URODYNAMIC STUDIES OF THE LOWER URINARY TRACT

Rien J. M. Nijman

Although the definition of urodynamic studies as stated by the International Continence Society—"the assessment of the function and dysfunction of the urinary tract"—implies a sound scientific basis, the truth is different. The major drawback that hampers the development of a real urodynamic science lies in the fact that no theoretical model exists to explain the results of measurements on the urinary tract.[1]

Many attempts to develop such a model have been published, but all of them either isolate some functional aspects or describe the function of separate organs in an isolated state. The classic urodynamic investigation of the lower urinary tract is an example of such an isolated study. It is aimed at diagnosing the storage and emptying functions of the bladder and urethra. Although regulatory influences of the central nervous system on these functions are acknowledged, the interpretation of the urodynamic findings is still based on a binary mode of nervous input: the bladder and, in part, the urethra are supposed to be either completely inhibited or completely activated by their nerves.

Nevertheless, urodynamic investigations are the cornerstone in the evaluation of bladder dysfunction in children with congenital or acquired malformations such as myelomeningocele, vesicoureteric reflux (VUR), posterior urethral valves, and urinary incontinence.[2-7] They are also important for proper management in children with neurologic disorders or imperforate anus.[8]

During the 1990s, urodynamic studies increased awareness and understanding of the pathophysiology of dysfunctional voiding, urge syndrome, and underactive bladder. Many pediatric urologists no longer feel the need to perform such invasive studies in all children. The diagnosis in many cases is based on the medical history, bladder diary, uroflowmetry, and determination of residual urine with ultrasonography. The availability of the bladder scan has made determination of residual urine after voiding much easier.

The combination of urodynamic investigations with fluoroscopy has been particularly promoted. The additional information provided by this so-called video-urodynamic investigation is such that it has become the standard in many institutions worldwide. Voiding cystograms as a separate study are no longer required, and the amount of radiation exposure has been significantly reduced through the use of modern equipment with memory facilities.

At present, various modalities are available to perform urodynamic investigations. The simplest tests are uroflowmetry and filling cystometry; more sophisticated methods are filling and voiding cystometry with electromyography (EMG) and fluoroscopy, and ambulatory urodynamics.

STANDARDIZATION OF TERMINOLOGY

Standardization of terminology and methodology should facilitate comparison of results by investigators using urodynamic methods in children. The definitions of the International Children's Continence Society (ICCS) as published by their Standardization Committee are used in this chapter.[9]

Classification and definition of incontinence are discussed in Chapters 27 and 28, as is the more detailed clinical workup of these patients. In all children with voiding disorders, a detailed history, physical examination, and quantification of urine loss should be performed before urodynamic investigation is initiated.

Bladder function can be described in terms of storage function and voiding function. Most children undergo uroflowmetry before a full urodynamic investigation is performed.

UROFLOWMETRY

The uroflow should be analyzed in detail in all children with urinary incontinence, recurrent urinary tract infections, or other voiding disorders. The graphic registration, with a simple flow meter, of the urinary flow curve and rate is a standard office procedure. Several recordings may be needed to obtain consistency.

Because the flow rate depends on the voided volume, the force of detrusor contraction, and the outflow resistance, it cannot simply diagnose the cause of impaired voiding.

Although a modern flow meter is a simple device, it is not so simple to obtain a reliable flow curve. The child should be stimulated to come with a full bladder, which can be checked with ultrasonography. If the bladder is almost empty, the child should be asked to drink some water until the bladder is full enough for a reliable flow.

Definitions

The *voided volume* is the total volume expelled via the urethra.
The *maximal flow rate* is the maximum measured value of the flow rate.
The *average flow rate* is the voided volume divided by flow time (this is meaningful only if the flow is continuous and without terminal dribbling).
The *flow time* is the time over which a measurable flow actually occurs.
The *time to maximal flow* is the elapsed time from onset of flow to maximum flow.

The average flow rate, flow time, and time to maximal flow are of lesser importance than the voided volume and the flow pattern.

Test Setup

The test should be explained beforehand, and the best results are obtained when the child voids in a sitting position, although older boys may prefer a standing position. While the child is seated, care must be taken that proper support of the legs is provided—without pants and preferably with a toilet seat adapted to age, so that the child can completely relax

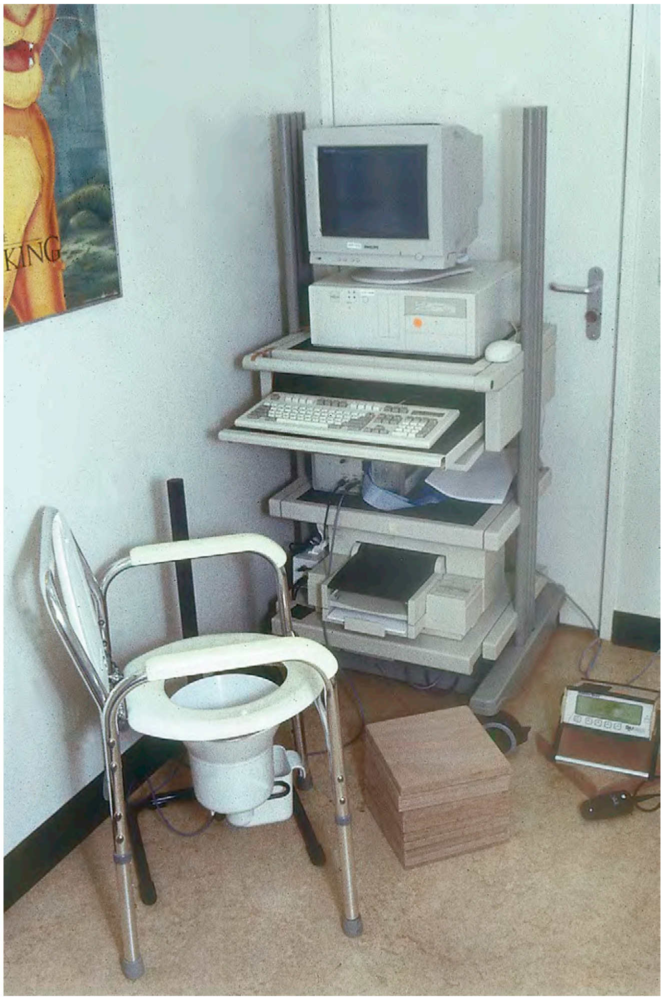

Figure 9-1 Setup for uroflowmetry: an adjustable chair; some blocks to give proper support; a real-time monitor, making the setup suitable for biofeedback training; a computer for storage and statistical analysis; a printer; and a bladder scan for residual urine measurement.

(Figs. 9-1 and 9-2).[10] When voiding, it is worthwhile to observe the child. Many children void with an abnormal posture. Small boys trying to void in a standing position sometimes have to stand on their toes (which makes relaxation of the pelvic floor muscles impossible) or squeeze their penis or have difficulty voiding through their zippers (it is better to let them take their pants down completely).

Flow Rates and Patterns

In children, normal flow rates are different from those in adults; in addition, there is much variation in flow rates among individuals.[11] The nomograms for adults cannot be used in children. Age should particularly be taken into account, because both bladder capacity and flow rate increase with age. Girls have higher flow rates than boys.[12-15]

In most children up to the age of 13 years, flow rates between 10 and 15 mL/sec do not necessarily mean abnormality.[16] Approximately 1% to 3% of school-age children have a voiding that can be labeled abnormal, with flattened or interrupted flow curves. The others have a normal, bell-shaped flow curve (Fig. 9-3).[17] It is not possible to consistently produce recordings using voided volumes of less than 50% of normal bladder capacity for age.

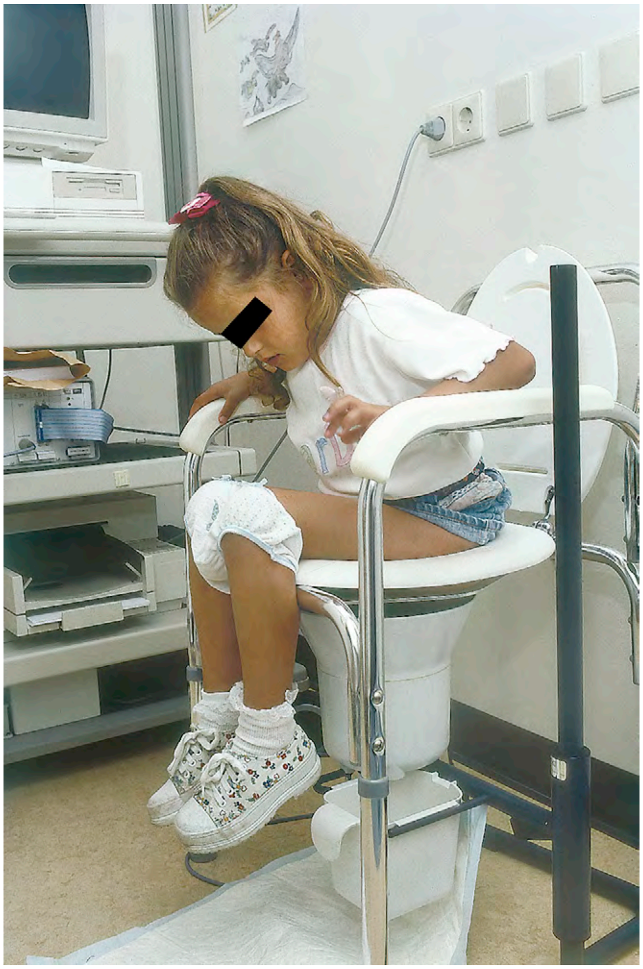

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Figure 9-2 Improper position on the toilet. Note that the legs are not supported. In this position, the pelvic floor muscles are not relaxed.

In children, a poor correlation exists between the maximal flow rate (Q_{max}) and the outflow resistance: an increase in outflow resistance is usually compensated by a strong detrusor contraction, resulting in an adequate Q_{max} but with the typical flow pattern of obstruction. However, a real anatomic obstruction is infrequently found in children; most of the obstructions have a functional nature, and, therefore, the pattern of the curve is most informative.

Urinary flow may be described in terms of rate and pattern and may be continuous, intermittent (in fractions), or staccato. In children with a so-called urge syndrome, the flow shows a normal pattern, but usually a less-than-normal volume is voided, whereas the Q_{max} may be very high. This is caused by a very strong detrusor contraction in combination with minimal or no outflow resistance.

An intermittent flow pattern shows an interrupted flow. In staccato voiding, the flow does not stop completely but fluctuates due to incomplete relaxation of the sphincter, as in dysfunctional voiding with poor relaxation of the pelvic floor muscles (Fig. 9-4). Sometimes, this finding is artifactual because the child stops voiding when urine is not directed into the collecting funnel. The pattern may also occur when abdominal straining is used to void (as in children with a *hypocontractile* bladder). To further evaluate discoordinated voiding, urinary flowmetry may be combined with a perineal EMG to demonstrate intermittent relaxation of the pelvic floor in combination with an intermittent flow pattern.

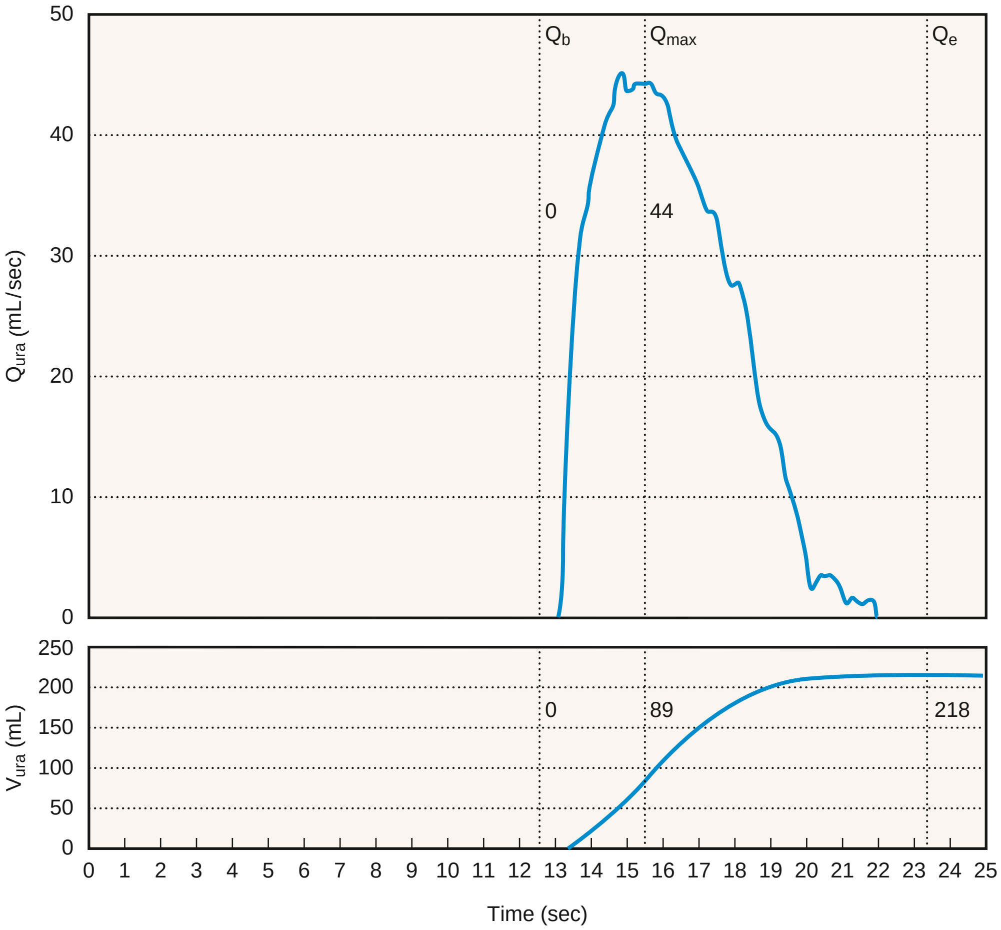


Figure 9-3 Normal flow curve. The maximal flow rate (Q_{max}) is 44 mL/sec; the voided volume is 218 mL. Q_b, start of flow; Q_e, end of flow; Q_{ura}, flow rate; V_{ura}, flow volume.

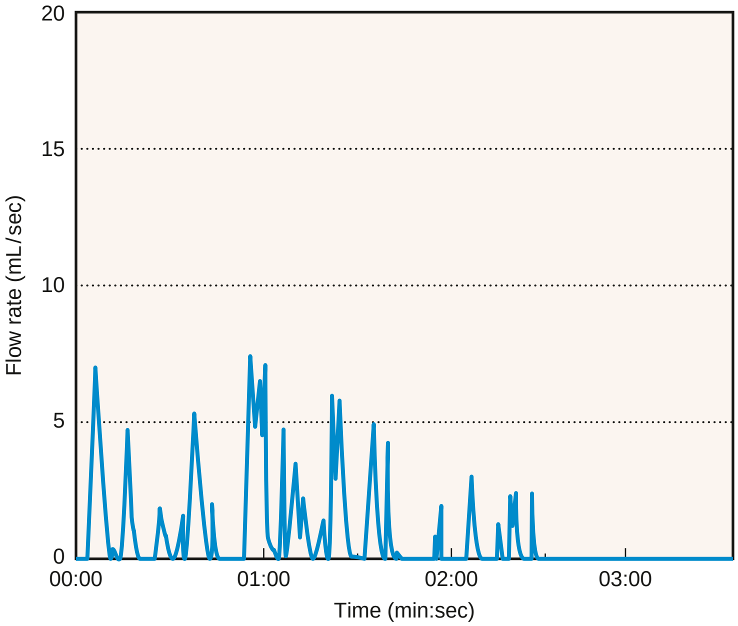


Figure 9-4 Interrupted flow curve in an 8-year-old boy with dysfunctional voiding. The maximal flow rate (Q_{max}) was only 7 mL/sec, and the residual urine volume was 78 mL. Note the different time scale: not in seconds, but minutes. Changing the setting of the time scale influences the shape of the flow pattern; even obstructed flows may seem nonobstructed if the time scale is compressed.

Interpretation

Measurement of urinary flow is performed either as an isolated procedure, with bladder filling by diuresis (spontaneous or forced), or as part of a pressure-flow study, with bladder filling by catheter. Patterns and rates should be consistent to allow for evaluation, and several recordings are needed to obtain consistency. The same parameters used to characterize continuous flow may be applicable, if care is exercised, in children with intermittent or staccato flow patterns. In measuring flow time, the time intervals between flow episodes are disregarded. Voiding time is total duration of micturition, including interruptions (see Fig. 9-4).

The study should be combined with an ultrasonographic study of the kidneys and bladder before and immediately after voiding, to detect residual urine. In addition, ultrasonography provides information on the influence of a full bladder on the degree of dilatation of the upper urinary tract. Both uroflowmetry and ultrasonography are noninvasive and can therefore be repeated at regular intervals to monitor the therapeutic results.

The results of flow studies should always be interpreted with care: all studies are complementary to the clinical findings. Normal findings do not rule out pathology, and abnormal studies do not necessarily reflect bladder dysfunction.

Postvoid Residual Volume

Except in small infants, the normal bladder will empty completely at every micturition.[18] The identification or exclusion of a postvoid residual volume is therefore an integral part of the study of micturition. However, when an uneasy child is required to void in unfamiliar surroundings, the results may be unrepresentative, and the same may be true for voiding on command with a partially filled or overfilled bladder. When estimating residual urine, the voided volume and the time interval between voiding and estimation of postvoid residual should be recorded. This is of particular importance if the patient is in a diuretic phase.

In patients with gross VUR, urine from the ureters may enter the bladder immediately after micturition and may falsely be interpreted as residual urine. The same phenomenon may be observed in those children who have dilatation of the upper tracts (megaureters) that depends on the degree of bladder filling. Even without reflux, the upper tracts dilate when the bladder fills, because increasing pressure in the bladder causes the ureters to dilate. As soon as the bladder is emptied, the pressure decreases, and the ureters expel the urine into the bladder. On ultrasound, the bladder appears full, whereas the dilatation of the ureters and sometimes the kidneys is diminished. This test may help to distinguish between obstructive and nonobstructive megaureter and should be done immediately after the child has voided.

The absence of residual urine is an observation of clinical value but does not exclude bladder outlet obstruction or detrusor-sphincter dysfunction with absolute certainty. An isolated finding of residual urine requires confirmation before being considered significant, especially in infants and young children.

Ultrasound-Flow-Ultrasound

This combination of imaging and noninvasive urodynamics is a standardized procedure used to obtain representative data on both flow rate and flow pattern, as well as postvoid residual volume. Bladder filling is assessed with ultrasound; when the bladder capacity is equal to the functional or expected capacity for age, the child is asked to void into the flow meter. After the flow is recorded, the postvoid residual is assessed again by ultrasound. This procedure avoids the registration of flow rates at unrealistic bladder volumes.

Alternatively, children can be asked to use a flow meter at home. A special flow meter has been designed for this purpose. This option can overcome any difficulty the child has voiding in a strange environment.

The use of a flow meter in combination with real-time monitoring offers the advantage that the child can actually see how she or he is voiding (Fig. 9-5). Biofeedback as a treatment modality for children with dysfunctional voiding is based on this concept and has proved to be highly effective.[19]

BLADDER CAPACITY

In order to interpret the findings with various urodynamic modalities, it is necessary to be able to estimate normal bladder capacity for the child's age and gender. Numerous attempts have been made to develop linear formulas to calculate bladder capacity. The difficulty is that many anatomic variables change in a nonlinear way with respect to age, height, and weight in the growing infant and child. In general, bladder capacity increases during the first 8 years of life at a rate of about 30 mL/year. Therefore, with an average capacity of 30 mL in the neonatal period, a child's bladder volume can be roughly calculated as $Y = 30(\text{Age}) + 30$ mL, where Y is the bladder capacity in milliliters and Age is the child's age in years.

Attempts at estimating bladder capacity accurately in children have been published by Koff,[20] Berger and coworkers,[21] Hjälmas,[22] Fairhurst and colleagues,[23] and others, but they all have flaws. The Berger[21] and Koff[20] formulas estimated bladder capacity in ounces ($Y_{oz} = \text{Age} + 2$ oz), using data obtained from children under general anesthesia. Koff used urodynamic measurements, whereas Berger and coworkers infused saline solution by hand at pressures of approximately 60 cm H_2O. Fairhurst[23] determined the bladder capacity in milliliters to be equal 7 times the child's weight in kilograms; this formula was derived by injecting contrast medium with a syringe during a voiding cystography until there was a leak around the catheter. In none of these studies were intravesical pressures recorded.

The formula for bladder capacity (in milliliters) used by Hjälmas[22] in infant boys (up to 2 years of age) was $Y = 24.8(\text{Age}) + 31.6$ mL; in infant girls, it was $Y = 22.6(\text{Age}) + 37.4$ mL. For older children, the formula $Y = 30(\text{Age}) + 30$ mL was used.

Kaefer and associates[24] calculated capacity in ounces and used the formulas $Y_{oz} = 2(\text{Age}) + 2$ oz for children younger than 2 years old and $Y_{oz} = \text{Age}/2 + 6$ oz for older children. Their studies used radionuclide cystography in which the capacity was determined when the child became uncomfortable or voiding occurred.

In 1999, a group in Japan[25] found that, because Japanese children appear to have somewhat smaller bladders, the best formula for bladder capacity (in milliliters) in that population was $Y = 25(\text{Age} + 2)$.

Another approach was described by Houle and coworkers.[26] They determined what volume of urine a child could normally store in the bladder at a safe pressure. The minimal acceptable total bladder capacity was determined to be 16 times the child's age in years + 70 mL.

Landau and colleagues[27] determined bladder capacity in children with neurogenic bladders at safe pressures; the minimal accepted capacity was found to be 18 times age in years + 45 mL.

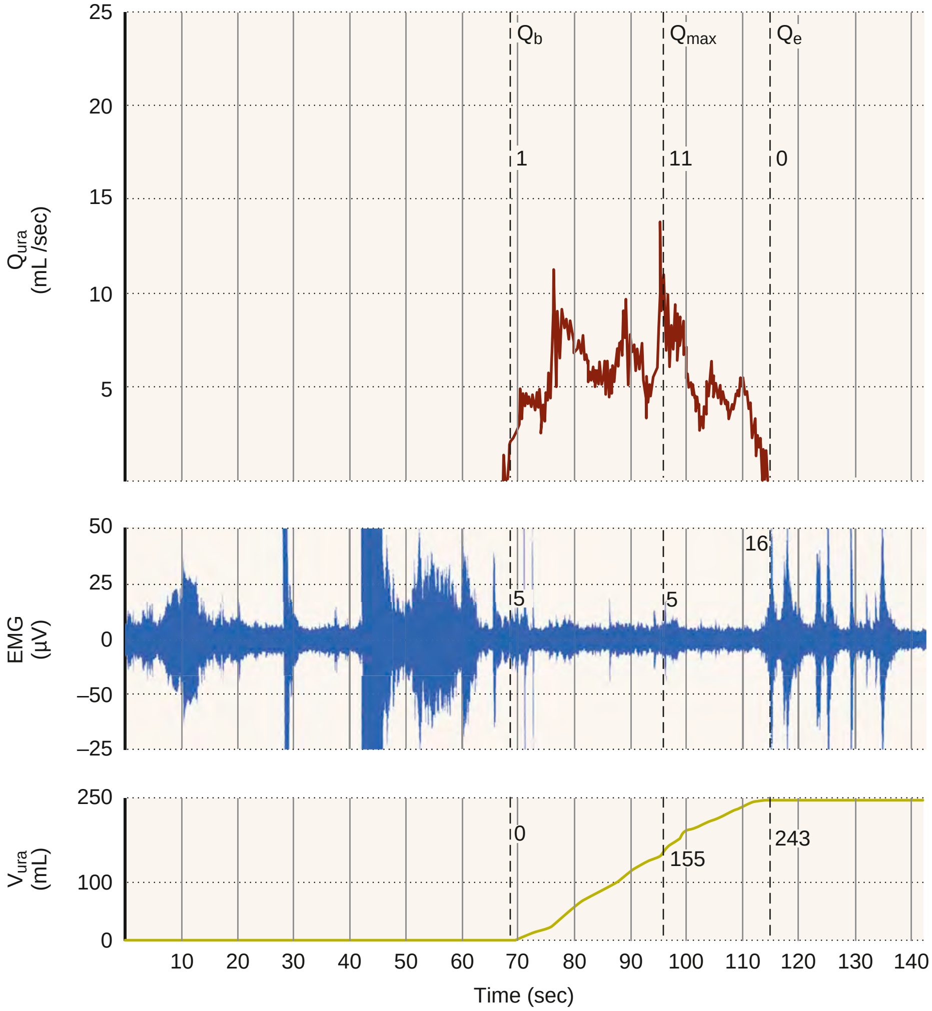


Figure 9-5 Example of a flow curve combined with pelvic floor muscle electromyography (EMG). The flow curve is of the staccato type (there is intermittent relaxation of the pelvic floor muscles, but the flow does not stop completely). This pattern can be seen in children with dysfunctional voiding and discoordination between detrusor contraction and sphincter relaxation. Q_{ura}, flow rate; V_{ura}, flow volume.

CYSTOMETRY AND VIDEO-URODYNAMICS

During cystometry, the pressure-volume relationship of the bladder is measured. This study provides information on the storage function (detrusor activity, sensation, compliance, and cystometric capacity) as well as the voiding function (outflow obstruction, flow pattern, and detrusor contractility). To evaluate the voiding function, it is best to place the patient in a sitting position. In newborns, therefore, only the storage function can be evaluated. Voiding can be observed as well, but pressure-flow studies are not feasible at that age.

The combination of cystometry with perineal EMG using skin electrodes provides information regarding pelvic floor activity during both filling and voiding.

Cystometry in combination with *fluoroscopy* is referred to as a *video-urodynamic study:* both the fluoroscopic images and the urodynamic findings are recorded (Fig. 9-6). The advantages are evident: during the investigation, the shape of the bladder (during both filling and voiding), the moment at which VUR occurs (at what volume and what pressure), and the influence of voiding on reflux can be monitored, as well as the configuration of the urethra and pelvic floor during voiding. In neurogenic bladders, not only is the shape of the bladder important but also, in many cases, the bladder neck appears to be insufficient during the filling phase, adding extra information with regard to possible causes of incontinence. Radiologic visualization of the urethra during voiding usually is more accurate than the EMG or measurement of urethral pressure in cases of urethral "overactivity."

Urodynamic investigation is an invasive procedure, and one must be aware of some artifacts that may influence the interpretation of the results of the examination.[28] It is not a natural situation, and most children are anxious to varying degrees. A transurethral catheter may influence voiding, and in some children the catheter "irritates" the bladder, inducing overactivity (a suprapubic catheter may eliminate the first problem, but not the second). The filling rate and temperature of the saline solution or contrast medium may also influence detrusor activity during both filling and voiding. Certain precautions must be observed: the filling rate should not exceed 10% bladder volume per minute, with a recommended maximal filling rate of 10 mL/min (physiologic filling). In cases of severe overactivity or diminished compliance, the filling rate is best reduced to 5% of bladder capacity per minute. The fluid used to fill the bladder (contrast medium or saline solution 0.9%) should be at 25° to 36° C. The bladder capacity is based on the maximum capacity noted on the bladder diary; therefore, before a urodynamic study is performed, the child

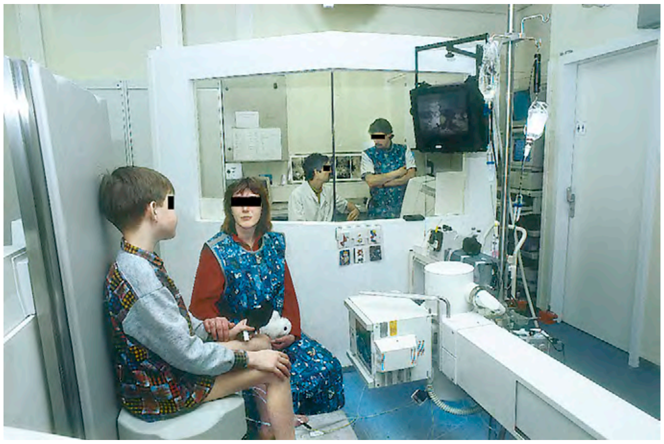


Figure 9-6 The setup for video-urodynamics. Note that the table is in the vertical position with a seat attachment (adjustable according to age). Underneath the seat is the flow meter; the feet are supported.

should keep a diary for 2 to 3 days. In most children, the first morning void shows the greatest volume.

To reduce anxiety, the study is best performed with the child in a sitting position watching a videotape or DVD together with one or both parents. All additional equipment that may increase anxiety should be removed from the room. The study should not be performed with the child under general anesthesia, but the use of intranasal midazolam does not appear to have a significant effect on the outcome of urodynamic studies.[29] In most children, a transurethral catheter can be used for bladder filling and pressure recording. The use of suprapubic catheters has not proved to be of additional value, but in selected cases, it may be necessary to place a suprapubic catheter to conduct the study. Transurethral catheters (7F [2.31 mm]or 8F [2.64 mm]) do not seem to have a significant obstructive effect in the urethra.[30,31]

Before the catheter is inserted, a free flow is obtained (the child is instructed to come with a full bladder); after voiding is completed, a transurethral catheter is inserted and residual urine is measured. For bladder filling and pressure measurement, a 6F (1.98-mm) or 7F double-lumen catheter is used; for rectal pressures, an 8F feeding tube can be employed (Fig. 9-7). Among microtip transducer catheters, the diameters of the catheters are similar, although the smallest size available is a 3F (0.99 mm); especially in boys, the introduction is not always easy. Usually, two or three complete filling and voiding phases are recorded.[32] Fluoroscopy is used at 30- or 50-mL intervals, during pressure increase, during reflux, and during voiding. Especially in cases of VUR, this combined examination is extremely useful. Bladder volume and pressure can be determined exactly at the time reflux occurs, making it easier to determine bladder capacity (particularly in grade VI to V reflux with dilated upper systems) and the influence of detrusor overactivity on the occurrence of reflux. The same is also true for the voiding phase: the shape of the bladder and bladder neck during voiding provides information that cannot be obtained otherwise. Poor relaxation of the pelvic floor muscles and urethral overactivity, as well as residual urine, can be easily detected.

To study the activity of the pelvic floor muscles in children, surface electrodes are widely used. They are positioned symmetrically left and right from the external anal sphincter. Because of resistance to electrical current across the skin electrode interface, the skin should be degreased (with alcohol) and desquamated skin should be removed (with abrasive paper) before the conductive gel and electrodes are applied.

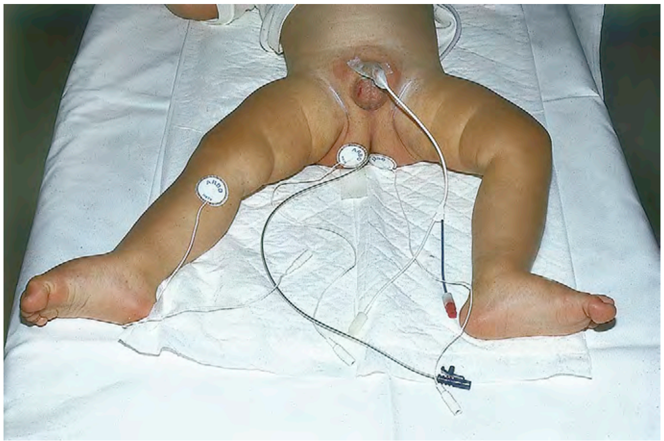


Figure 9-7 A double-lumen 6F (1.98-mm) or 7F (2.31-mm) catheter is inserted into the bladder and fixed to the penis. An 8F (2.64-mm) feeding tube is used for rectal pressure recording. The catheters are connected to external pressure transducers, the filling channel to a pump. The skin electrodes are later covered with Tegaderm to prevent their becoming wet.

The use of an x-ray memory limits the exposure time; in our experience, the average time is 0.45 minute for a complete study, making the total amount of radiation exposure less than that of a plain radiograph of the abdomen.

Definitions and Classification

Assessment of the Storage Phase

For assessment of the storage phase, the following pressures are measured:

Intravesical pressure (P_{ves}): the pressure within the bladder
Abdominal pressure (P_{abd}): the pressure around the bladder, derived from rectal pressure obtained by a perfused 8F feeding tube or microtip catheter placed in the rectum
Detrusor pressure (P_{det}): obtained by subtracting the abdominal pressure from the intravesical pressure (with modern urodynamic equipment, this is done electronically)

When the patient is in the sitting position, both intravesical and abdominal transducers will record a higher hydrostatic pressure exerted by the abdominal components on the transducer membrane (about 15 cm H_2O higher than in the supine position), but the detrusor pressure should remain the same.

CAPACITY

In cases of sphincter incompetence or lack of bladder sensation, the maximum bladder capacity is difficult to determine. A Foley catheter may be used to occlude the bladder neck to determine the capacity; if there is lack of filling sensation, the clinician stops filling when the resting pressure in the bladder has reached 30 cm H_2O.

The *functional bladder capacity* is a more relevant parameter for the clinician. It is defined as voided volume and is estimated from the frequency/volume diary. Consistent values can be obtained if the child voids only when there is a genuine desire to void, but this can be achieved only when voiding is supervised.

SENSATION

In general, *bladder sensation* is very difficult to evaluate in children, and it can be a relevant parameter only in toilet-trained children. Previously used terms such as “first desire to void” or “strong

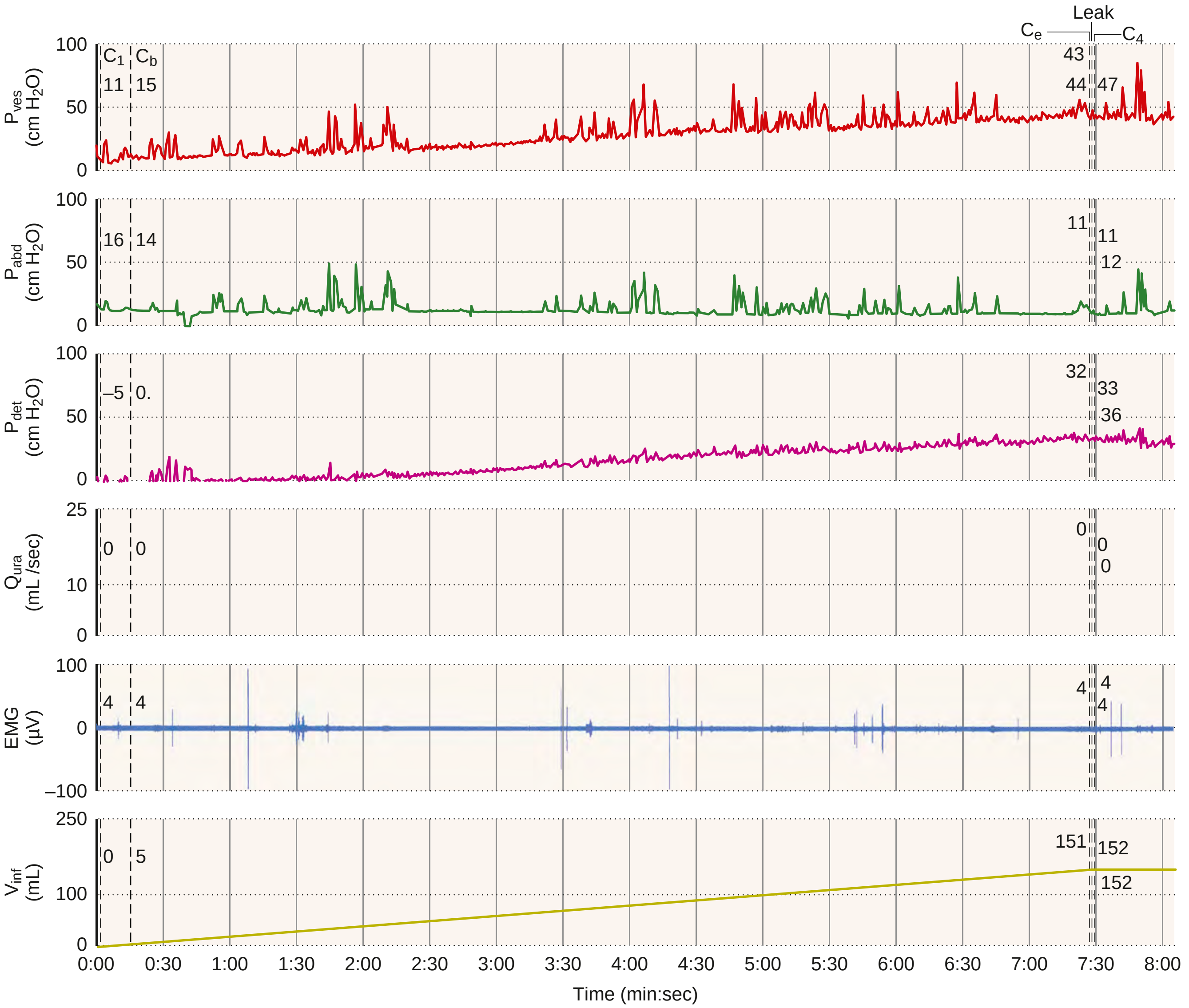


Figure 9-8 A urodynamic study in a 10-year-old girl with spina bifida. There is a gradual rise in detrusor pressure (P_{det}), indicating reduced elasticity of the bladder wall. The compliance is calculated between the points marked Cb and Ce (here, leakage occurred at leak-point pressure). The compliance is $\Delta V/\Delta P_{det}$ = 152/36, or 4.2 mL/cm H_2O. If the bladder were filled more slowly, the compliance might become normal. Diminished compliance is a typical finding in neurogenic bladders and in some infectious diseases (tuberculosis, bilharziasis). EMG, electromyographic activity; P_{abd}, abdominal pressure; P_{ves}, intravesical pressure; Q_{ura}, flow rate; V_{inf}, infused volume.

desire to void" may be of use in adults but are of no particular value in children. "Normal desire to void" is not relevant in the infant but may be used as a guideline in children age 4 years and older. It should be considered the volume at which some unrest is noted (e.g., wriggling of the toes); this usually indicates that voiding is imminent. In the older child, the volume may be small with the first cystometry, for fear of discomfort. This is the reason that at least two cycles of filling are recommended.

Bladder sensation can be classified as normal, increased (hypersensitive), reduced (hyposensitive), or absent.

COMPLIANCE

Bladder compliance indicates the relationship between change in bladder volume and change in detrusor pressure. It is calculated by dividing the volume change (ΔV) by the change in detrusor pressure (ΔP_{det}) during that change in bladder volume ($\Delta V/\Delta P_{det}$) and is expressed as milliliters per centimeter of water (mL/cm H_2O) (Fig. 9-8).

Especially when severe detrusor overactivity is present, it may be difficult to determine compliance. To standardize measurements, the most linear part of the pressure-volume relationship should be marked off on the cystometrogram. The values for P_{det} and V_{inf} at the beginning and end of that part are then used to capture $\Delta V/\Delta P_{det}$. The usual notation for compliance is the single value, but in children, the full notation (i.e., both volume and pressure values) may be helpful.

Compliance is variably dependent on the following factors:

Rate of bladder filling
Part of the curve used for compliance calculation
Shape (configuration) of the bladder
Thickness of the bladder wall
Mechanical properties of the bladder wall
Contractile and relaxant properties of the detrusor

If little or no pressure change is noted during a normal bladder filling, the compliance is called *normal*. There are no

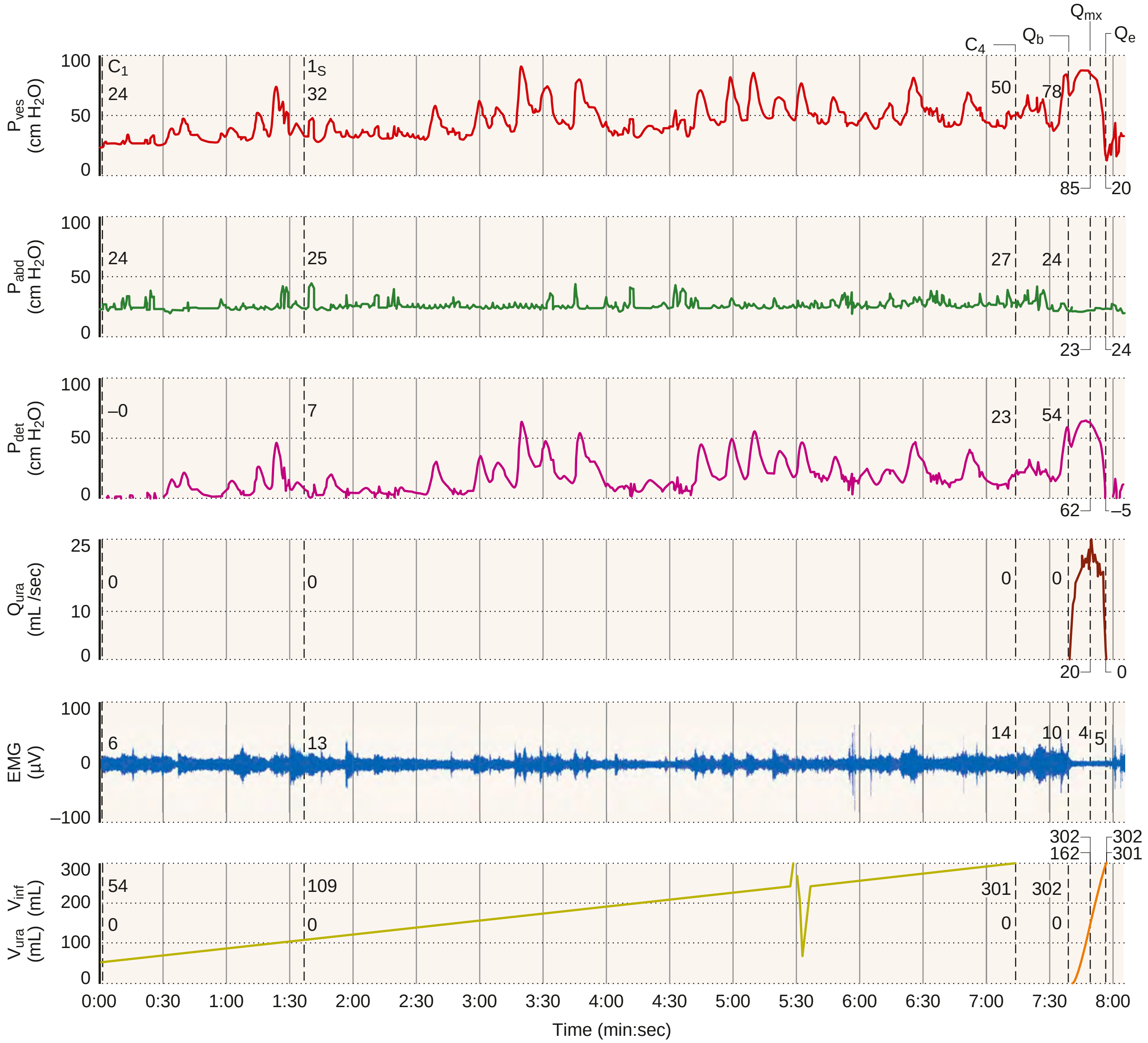


Figure 9-9 A urodynamic study showing severe detrusor overactivity during filling. Note that each detrusor contraction is accompanied by increased pelvic floor muscle electromyographic (EMG) activity. Voiding is complete with a detrusor pressure (P_{det}) of 62 cm H_2O and good relaxation (no visible EMG activity) and without abdominal straining (no increase in P_{abd}). P_{ves}, intravesical pressure; Q_{ura}, flow rate; V_{inf}, infused volume; V_{ura}, volume voided.

data available to exactly determine a normal compliance, nor a high or a low compliance. It is important not only to note the compliance but also to mention the rate of bladder filling, the volume at which compliance was calculated, and which part of the curve was used.

In children without neurologic problems, compliance should not exceed 0.05Y mL for each centimeter of increase in the baseline bladder pressure, where Y is the cystometric bladder capacity for age (see earlier discussion).

DETRUSOR ACTIVITY

Detrusor activity is interpreted from measurement of the detrusor pressure (P_{det}). It may be normal, overactive, or underactive.

In the normal situation, bladder volume increases during filling without significant rises in P_{det}. This process is called *accommodation*. Even after provocation, there are no involuntary contractions. The "normal" detrusor is described as *stable*. Involuntary detrusor contractions during the filling phase (spontaneous or provoked) are characteristic for detrusor "overactivity" (Fig. 9-9). The child cannot completely suppress these contractions; usually, an increase in pelvic floor EMG activity is noted as counteraction. Rapid filling, anxiety, alterations of posture, coughing, walking, jumping, and other triggering procedures may provoke involuntary contractions. Involuntary detrusor contractions may be asymptomatic, or they may be interpreted as a normal desire to void. In infants, these detrusor contractions often occur

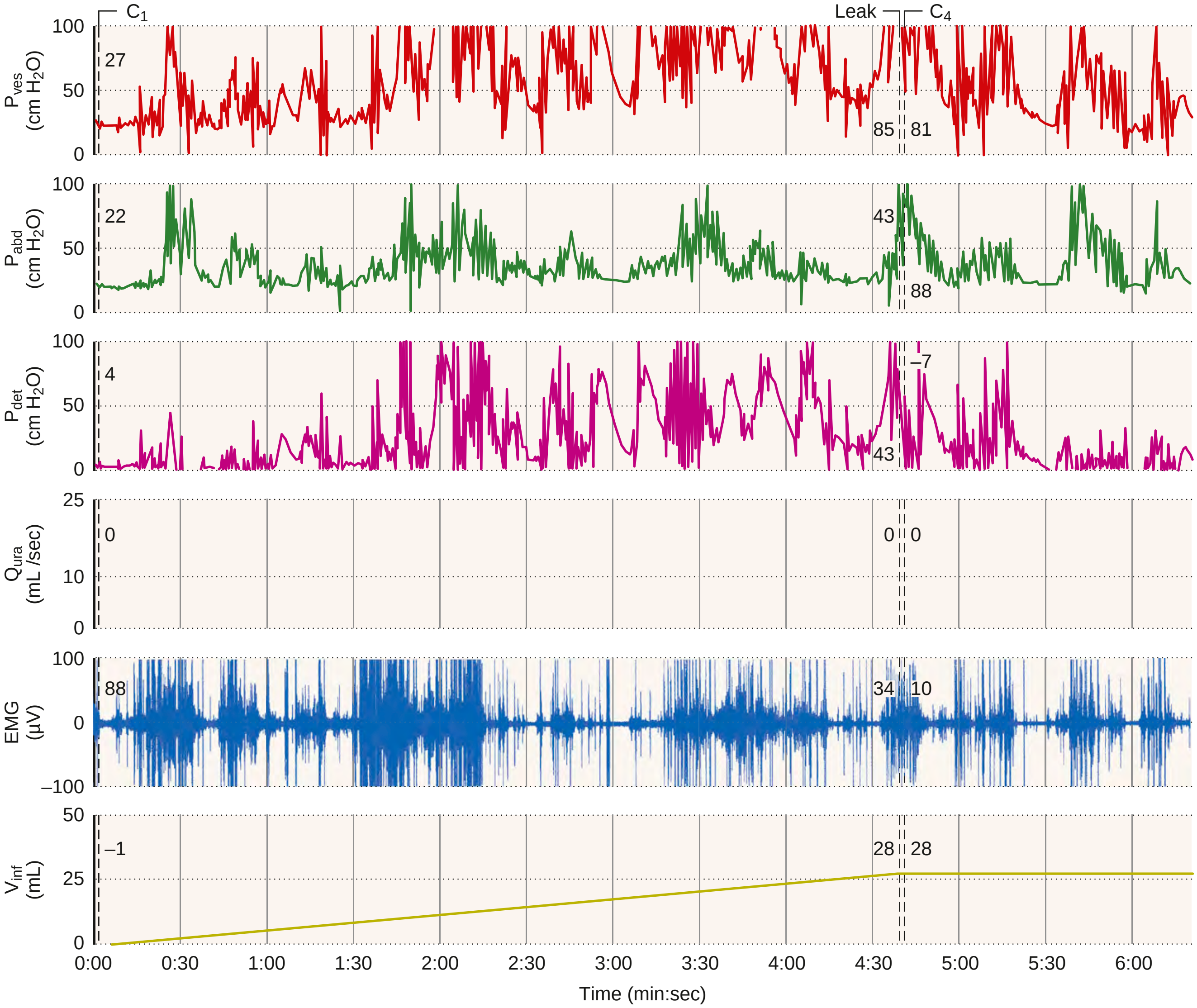


Figure 9-10 A 2-year-old girl with a tethered cord. Severe overactivity of the detrusor occurs because of the neurologic lesion. In combination with an overactive pelvic floor, these high pressures without normal voiding (some dribbling of urine is usually seen) are typical for detrusor sphincter dyssynergia. EMG, electromyographic activity; P_{abd}, abdominal pressure; P_{det}, detrusor pressure; P_{ves}, intravesical pressure; V_{inf}, infused volume.

throughout the filling phase. Overactivity resulting from a disturbance of the nervous control mechanisms is called *neurogenic detrusor overactivity* (formerly known as "hyperreflexia") (Fig. 9-10).

If no detrusor contraction is seen at the end of the filling phase, the detrusor is *underactive*. It may be noticed in the overdistended postobstructive bladder and may lead to a risk of overfilling the bladder during the study. It may also occur in children with a so-called underactive bladder (formerly known as "lazy bladder").

LEAKAGE

The normal urethral closing mechanism maintains a positive urethral closure pressure (guarding reflex).[33] Shortly before micturition, the normal closure pressure decreases to allow flow. An *incompetent closure mechanism* is defined as one that allows leakage of urine in the absence of a detrusor contraction. In genuine stress incontinence, leakage occurs when the intravesical pressure (Q_{ves}) exceeds intraurethral pressure (Q_{ura}).

To clinically define the bladder with high pressures at small capacity, the term *leak-point pressure* has been introduced. This is the detrusor pressure (at any given volume during the filling phase) at which the first drops of urine pass the meatus. Pressures lower than 40 cm H_2O are considered acceptable.[34]

In children, the transition from filling phase to voiding phase is not as marked as in adults. To avoid missing this important transition, cystometry and pressure-flow/EMG measurements are performed as one continuous study in pediatric urodynamics.

Assessment of the Voiding Phase

The detrusor during voiding may be acontractile, underactive, overactive, or normal. Normal voiding is achieved by a voluntarily initiated detrusor contraction that is sustained

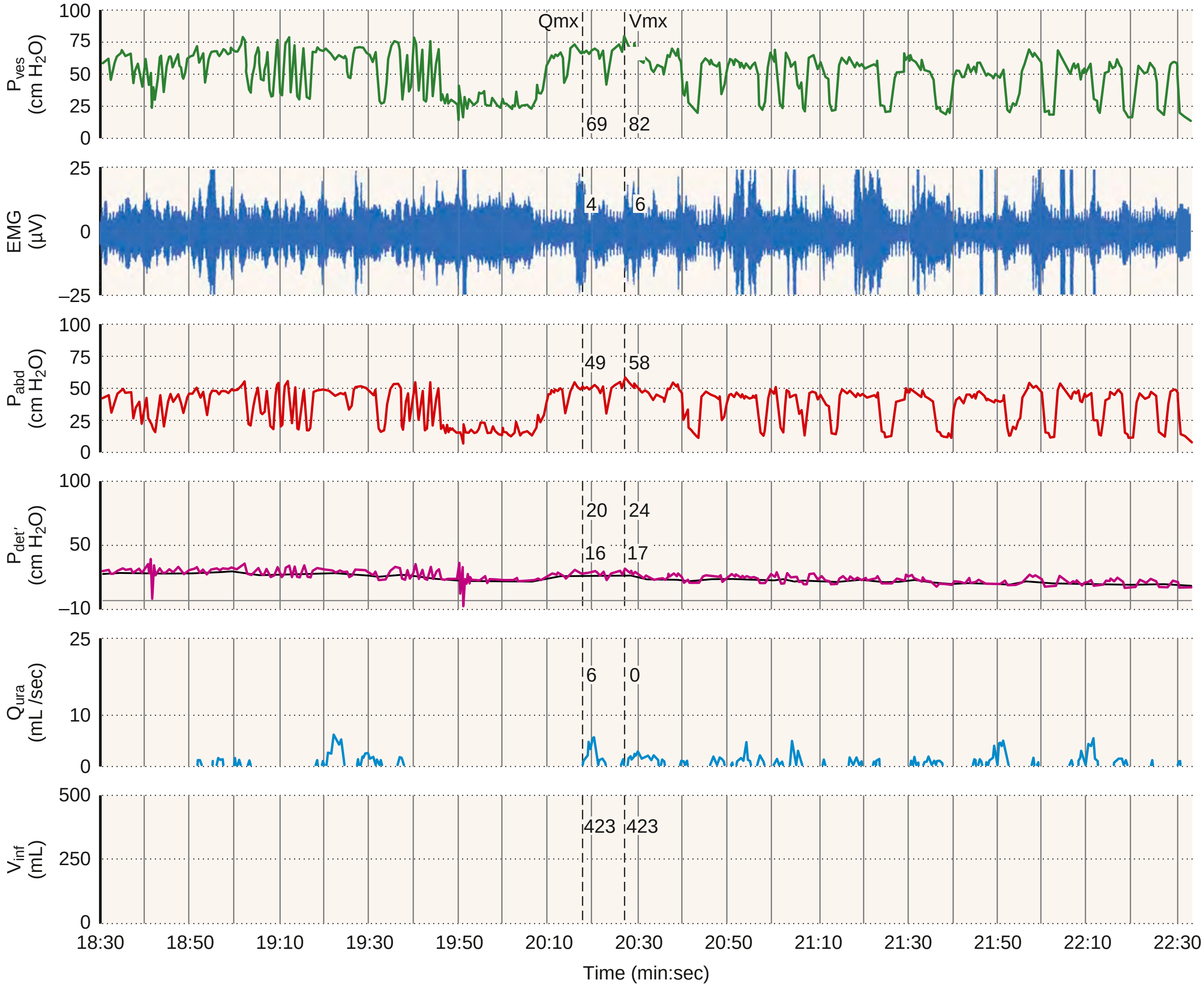


Figure 9-11 A urodynamic study in a 12-year-old boy with voiding difficulties, urinary tract infections, and incontinence. During the filling phase, no detrusor action is recorded; voiding takes place only with abdominal straining (increased P_{abd}) and no visible detrusor contraction (P_{det}). Note that pelvic floor muscle activity (EMG) is increased with each straining effort. There was significant residual urine volume, and the flow pattern was intermittent and prolonged. This is an example of a so-called underactive bladder. P_{ves}, intravesical pressure; Q_{ura}, flow rate; V_{inf}, infused volume.

and cannot usually be suppressed voluntarily. In the absence of bladder outlet obstruction, a normal contraction will empty the bladder completely. Available reports on detrusor pressures during voiding in normal children give a wide range, from 66 cm H_2O in boys and 57 cm H_2O in girls to normal adult values.[35] These pressures are lower than those reported by Yeung and associates,[36] who found pressures in boys to be 118 cm H_2O, and in girls, 75 cm H_2O.

The acontractile detrusor does not demonstrate any activity during the voiding phase in a urodynamic study (Fig. 9-11). If acontractility is caused by a neurologic problem, it is called *detrusor areflexia*. This term denotes the complete absence of centrally coordinated contraction. Other terms (e.g., hypotonic, autonomic, flaccid) should be avoided. If the detrusor contraction is of inadequate magnitude and duration to effectively empty the bladder, the condition is referred to as *detrusor underactivity during voiding*.

The urethra during voiding may be normal or obstructive. The normal urethra opens during voiding to allow the bladder to be emptied. Obstructive urethral function may be caused by overactivity of the sphincteric mechanism or by anatomic obstruction (e.g., posterior urethral valves, stricture) (Figs. 9-12 and 9-13).

An *anatomic obstruction* creates a urethral segment with a small and fixed diameter that does not dilate during voiding. As a result, the flow pattern is plateau shaped, with a low and constant maximum flow rate despite high detrusor pressure and complete relaxation of the urethral sphincter. In a *functional obstruction*, it is the active contraction of the urethral sphincter during passage of urine that creates the narrow urethral segment, constantly or intermittently. To differentiate anatomic from functional obstruction, information is needed about the activity of the urethral sphincter during voiding. This information can be obtained and recorded, together with pressure and flow, by monitoring the urethral pressure at the level of the urethral sphincter or by recording a continuous EMG of the striated urethral sphincter. For clinical purposes, if the urethral sphincter is not readily accessible, the EMG of the external anal sphincter is often used to monitor activity of the striated urethral sphincter. This corresponds to activity of the pelvic floor muscles. Also the use of video urodynamics can be very helpful in this respect, because contractions of the pelvic floor muscles can actually be seen during the voiding phase.

In small children and in those children who are afraid to void, "overactivity of the urethra" with residual urine may be a normal finding. In detrusor-sphincter dyssynergia, the detrusor contraction and involuntary contraction of the urethral and/or periurethral striated muscles occur simultaneously during micturition. This condition is by definition of neurogenic origin. If (over)activity of the urethral sphincter occurs during voiding in neurologically normal children, it is termed *dysfunctional voiding* or *discoordinated voiding*.

URETHRAL PRESSURE PROFILE

In stress incontinence, a urethral pressure profile may be of use; however, this is a rare anomaly in children (except in those with a neurogenic bladder). The profile is difficult to perform and interpret: pulling a catheter along the length of the urethral lumen at best provokes strong reflex activity of the

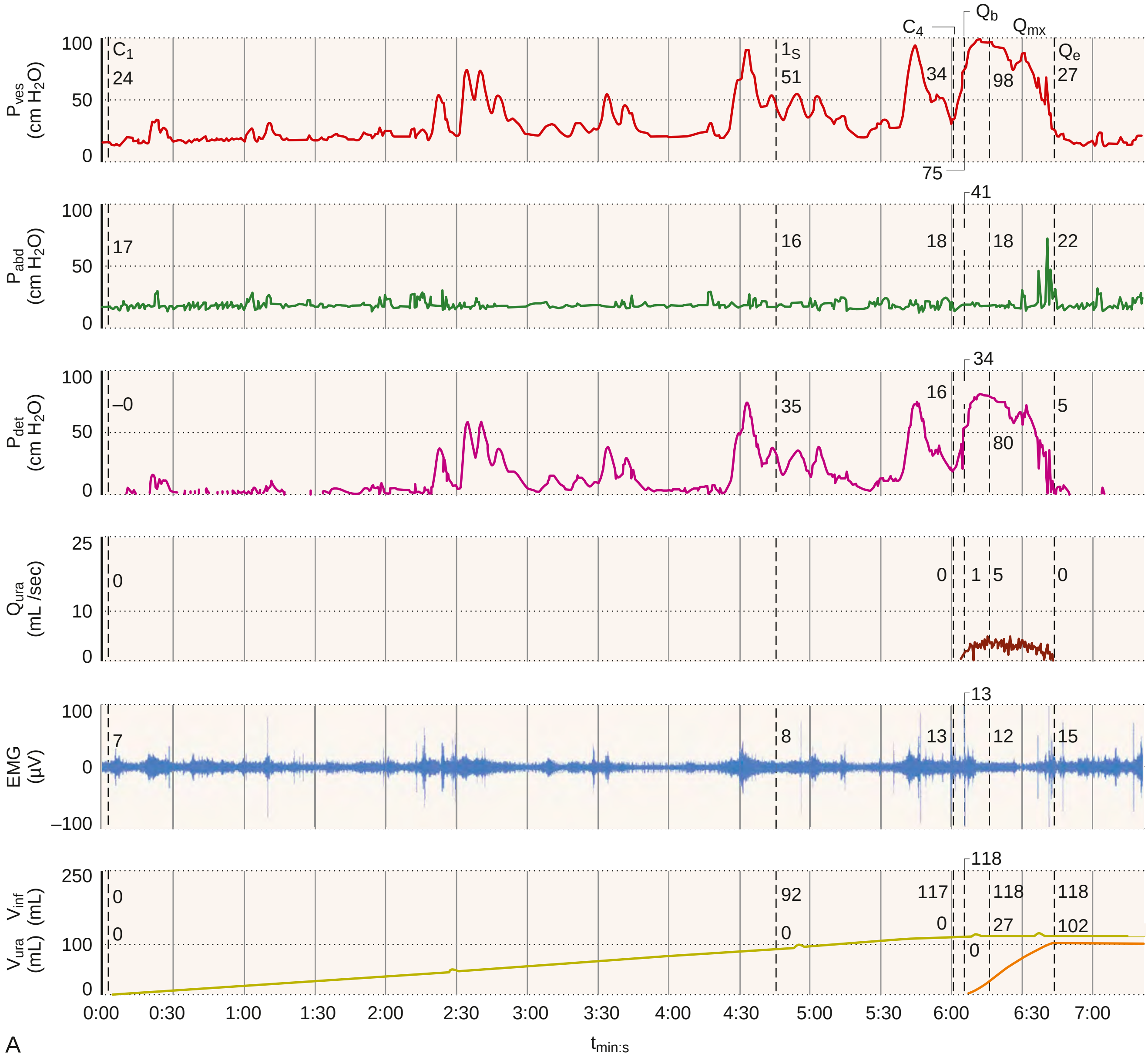


Figure 9-12 **A,** Urodynamic study 2 years after treatment for posterior urethral valves. There is significant detrusor overactivity as well as an obstructed flow. P_{abd}, abdominal pressure; P_{det}, detrusor pressure; P_{ves}, intravesical pressure; Q_{ura}, flow rate; V_{inf}, infused volume; V_{ura}, voided volume.

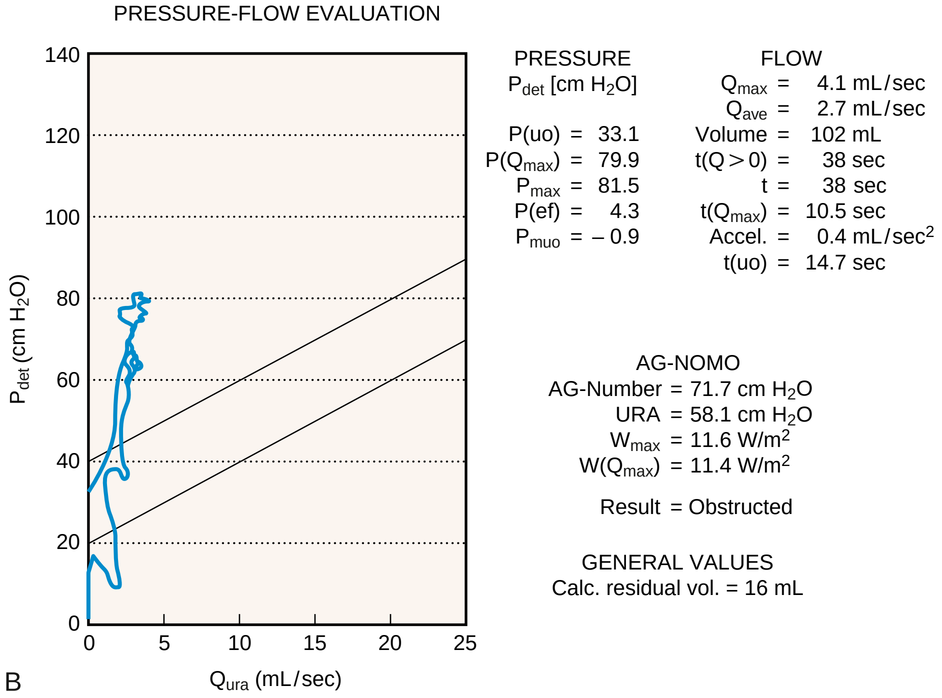


Figure 9-12, cont'd B, The pressure-flow evaluation shows high pressures (P_{det}) with low flow rates (Q_{ura}), consistent with an obstructive pattern. P_{max}, maximal pressure; $P(Q_{max})$, pressure at maximal flow rate.

pelvic floor muscles. Another problem is that it cannot provide reproducible quantification of urethral resistance or obstruction. Because it cannot discern between mechanical and functional obstruction, the urethral pressure profile is not routinely used in children.

AMBULATORY URODYNAMIC INVESTIGATIONS

At present, the use of 12- or 24-hour (natural fill cystometry) monitoring of bladder function in children is primarily of academic interest. It may provide some additional information in cases of neurogenic bladder or poorly understood urinary incontinence, but the overall benefits are limited. During the study, children are encouraged to do whatever they would normally be doing, but the consequence of "normal" behavior is that many times the catheters do not remain in the bladder or rectum. Children with strong detrusor contractions may expel the bladder catheter during voiding. Therefore, it is advised to perform this type of study during a short hospitalization period in day care or a 1-night stay.

INDICATIONS FOR URODYNAMIC INVESTIGATIONS IN CHILDREN

The most important indications for urodynamic investigations are as follows:

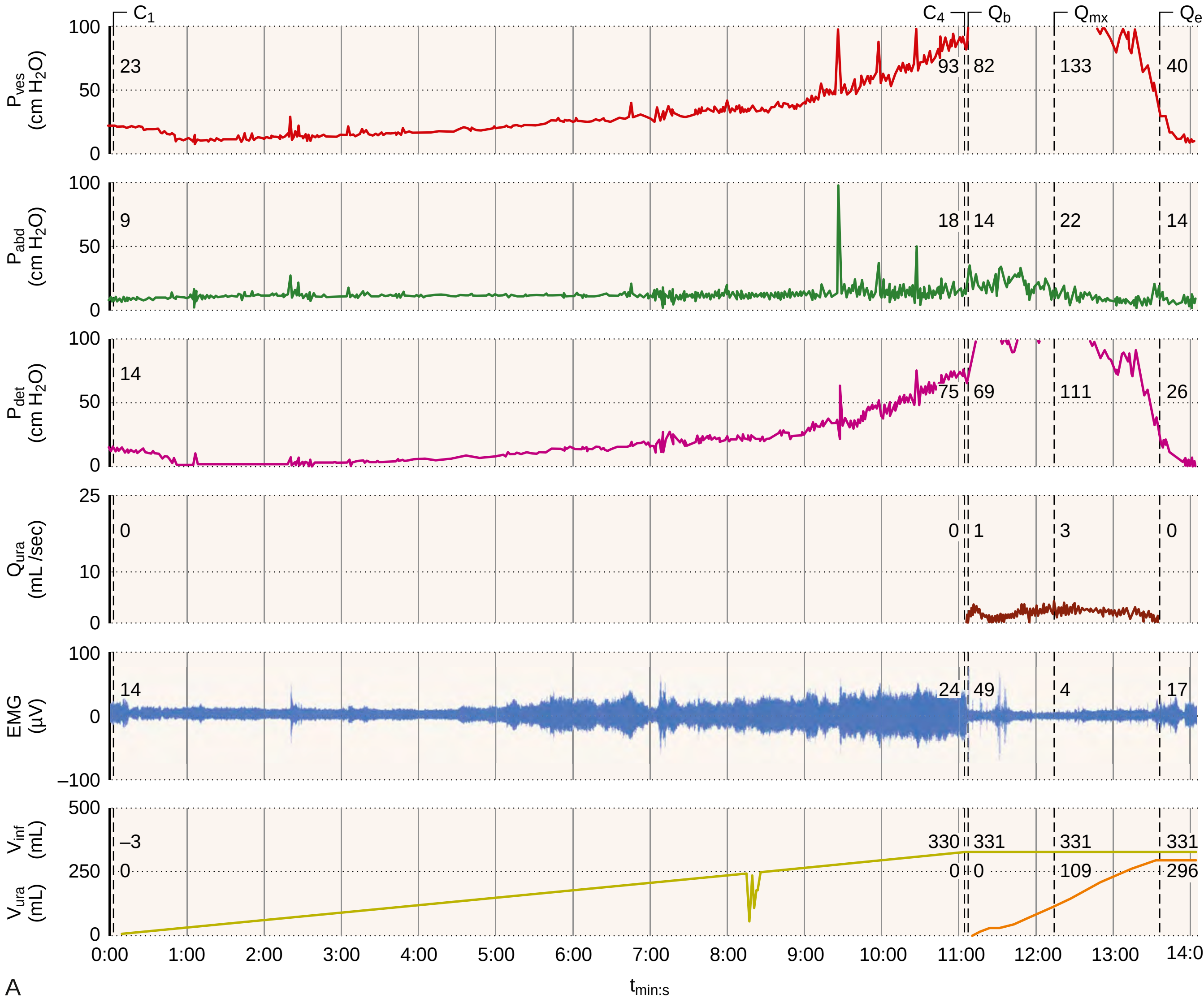
Neurogenic bladder (e.g., spina bifida, tethered cord)
Anorectal malformations
Voiding dysfunction, including urge syndrome and underactive bladder
Vesicoureteric reflux (VUR)
Urinary incontinence
Infravesical obstruction
Obstructive uropathy

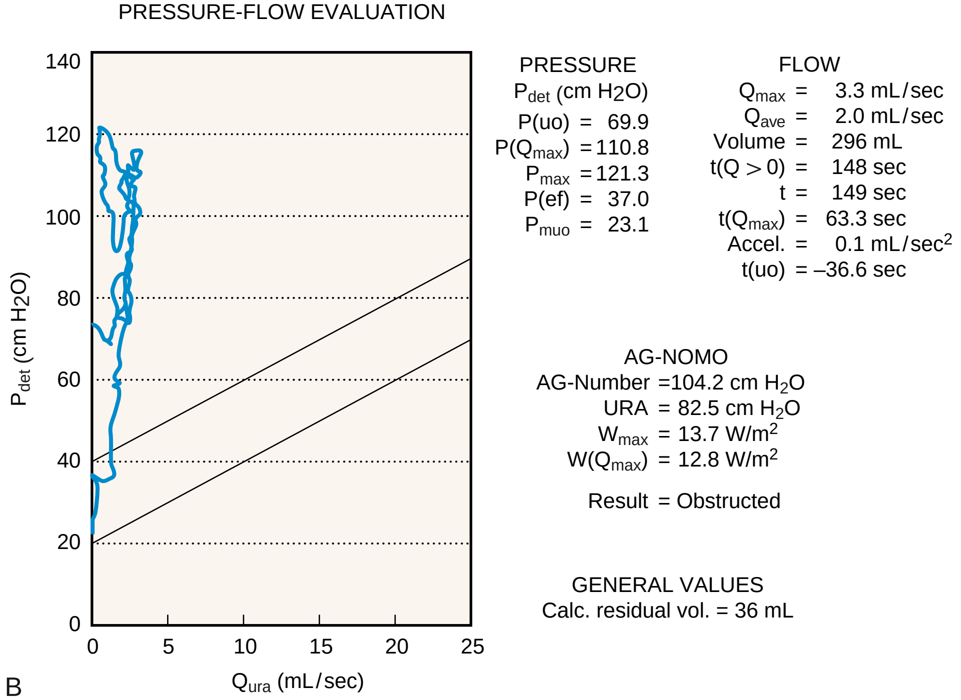
The evaluation of bladder dysfunction after posterior urethral valve ablation or resection is another example of the significant role urodynamics may play in the management of such conditions.

CLINICAL IMPLICATIONS

Urodynamic investigations should be conducted only if a treatment strategy has been defined beforehand. Without implications, such a study should not be performed. Table 9-1 lists some of the clinical urodynamic implications.[37,38]

Urodynamic studies in children are best performed by the urologist. To obtain a complete picture, one has to be present during the investigation to see how the child behaves during the study and also to monitor the parents. This observation provides an ideal opportunity that may completely alter the treatment protocol. Another advantage is that, after a while, history taking and initial workup will be more accurate and specific, and a lot of extra investigations may be avoided. This is also an important factor, because urodynamic investigations are invasive, the surroundings are frightening, and, although the parents may be present, the whole procedure remains quite unnatural to the child. Not all children can void with a transurethral catheter inserted, and sometimes they void only when everybody, including the parents, have left the room temporarily. The availability of a television, videocassette recorder, or digital videodisc (DVD) player is a major advantage, because the children may watch their favorite tape to distract them. For very small children, the parents are advised to bring a bottle and some toys.





PRESSURE
P_{det} (cm H_2O)
P(uo) = 69.9
P(Q_{max}) = 110.8
P_{max} = 121.3
P(ef) = 37.0
P_{muo} = 23.1

FLOW
Q_{max} = 3.3 mL/sec
Q_{ave} = 2.0 mL/sec
Volume = 296 mL
t(Q > 0) = 148 sec
t = 149 sec
t(Q_{max}) = 63.3 sec
Accel. = 0.1 mL/sec^2
t(uo) = –36.6 sec

AG-NOMO
AG-Number = 104.2 cm H_2O
URA = 82.5 cm H_2O
W_{max} = 13.7 W/m^2
W(Q_{max}) = 12.8 W/m^2

Result = Obstructed

GENERAL VALUES
Calc. residual vol. = 36 mL

Figure 9-13 **A,** A 12-year-old girl with urinary tract infections and incontinence after reconstruction for an ectopic ureterocele in childhood. Note the diminished compliance and extremely high voiding pressures with a very low flow rate. This is typical of an anatomic obstruction at the level of the bladder neck. EMG, electromyographic activity; P_{abd}, abdominal pressure; P_{det}, detrusor pressure; P_{ves}, intravesical pressure; Q_{ura}, flow rate; V_{inf}, infused volume; V_{ura}, voided volume. **B,** pressure-flow evaluation in the same child. Low flow rate in combination with very high voiding pressures indicate an anatomical obstruction (at the level of the bladder neck). P(Q_{max}), pressure at maximal flow rate.

Table 9-1 **Clinical Implications of Urodynamic Findings**

Diagnosis	Treatment
Reflux + instability	Anticholinergics
Poor compliance (neuropathic and valve/bladder)	Anticholinergics, augmentation
Residual urine	Voiding regimen, CISC
Infravesical obstruction	Cystoscopy + incision or resection
Urethral "overactivity"	Medical or behavioral modification
Poor relaxation/dyssynergia	Medical or behavioral modification

CISC, clean intermittent self-catheterization.

CONCLUSION

Urodynamic investigation has become a major tool in the evaluation of bladder dysfunction in many children. However, urodynamic investigation is invasive and, by definition, far from natural, and artifacts may influence to a great extent the correct interpretation of these studies. Furthermore, the studies do not always show reproducible results. Urodynamic studies are part of the whole diagnostic workup and must not be taken out of the right context.

In many cases, it is very tempting to "treat" the results of a urodynamic study rather than the actual condition in the individual child. Many such therapies will fail, and parents, doctors, and, most importantly, the children themselves will end up disappointed.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 10

URODYNAMIC STUDIES OF THE UPPER URINARY TRACT

Leo C. T. Fung*and Antoine E. Khoury

Hydronephrosis is defined as the dilatation of the urinary collecting system ("hydro," from Greek *hydor,* meaning water; "nephros," meaning kidney; and "osis," meaning condition). It can be associated with either an impediment in antegrade urinary flow or the retrograde reflux of urine. Among those kidneys that develop hydronephrosis as a result of some form of antegrade obstruction of the collecting system, there is a tremendous variability in the natural history observed. Whereas some kidneys undergo progressive irreversible renal injury, others remain stable for long periods or even undergo spontaneous improvement. For those hydronephrotic kidneys that have been identified as needing medical intervention, well-established surgical treatment is available. This treatment is effective in stabilizing or even improving renal function after successful surgical correction. Given that some hydronephrotic kidneys are at risk for renal injury and others are not, the current controversy in the clinical management of hydronephrosis lies not so much in how to treat the condition but rather in the identification of which kidneys require surgical treatment. There is currently no general consensus on how best to identify those hydronephrotic kidneys that are in need of surgical repair.

In this chapter, the role of upper urinary tract urodynamics is discussed in the context of the continuing pursuit of diagnostic tools to better identify hydronephrotic kidneys in need of surgical treatment. Because upper tract urodynamics pertains primarily to the evaluation of antegrade urinary flow, the discussion in this chapter is limited to hydronephrosis that results from the impediment of antegrade urinary flow. Dilatation of the collecting system that results from the retrograde reflux of urine, or vesicoureteral reflux (VUR), is addressed in other chapters in this textbook.

Hydronephrosis that results from an impediment in antegrade urinary flow is a highly complex process at the physiologic as well as the molecular level. However, it is fundamentally still a physical problem in which the collecting system has excessively high resistance to urine flow. The source of the problem is physical in nature, and the solution is also a physical one, in which the obstructive site is surgically corrected or mechanically bypassed. Recognizing that hydronephrosis is fundamentally a mechanical drainage issue, the diagnostic tools used in the evaluation of hydronephrosis can rely on one of two general principles: direct assessment of resistance to flow in the collecting system through measurement of physical parameters, including pressure and flow, and assessment of effects that occur secondary to the increased resistance to urine flow in the collecting system, including morphologic, physiologic, and functional alterations. Most of the currently available diagnostic tools belong to the second category, demonstrating effects secondary to the increased resistance to urine flow. For example, imaging modalities evaluate for dilatation of the collecting system proximal to the suspected site of obstruction. Contrast-enhanced studies may reveal delays in excretion of contrast material, and nuclear medicine renography differential renal function testing assesses for alterations in renal function. Although these diagnostic tests are noninvasive in nature and play important roles in the assessment of hydronephrosis, they do not address the fundamental issue of resistance to urine flow in the collecting system. In contrast, obstruction in the upper urinary tract can also be diagnosed by a direct demonstration of increased resistance to urine flow in the collecting system. Such direct mechanical evaluation of the efficiency of urine flow in the collecting system constitutes the primary objective of *upper tract urodynamic studies*.

Upper tract urodynamics encompasses the study of urinary transport efficiency and pressure-flow characteristics of the collecting system, originating anatomically at the renal calyces and ending at the ureterovesical junction (UVJ). In order to study urodynamic parameters of the upper urinary tract, access to the collecting system is customarily obtained via percutaneous nephrostomy needles or tubes; pressure and flow characteristics of the collecting system can then be evaluated. The diagnostic procedures that evaluate upper tract urodynamics can in general be referred to as *percutaneous pressure-flow studies* (Fig. 10-1). The evaluation of upper urinary tract urodynamics using percutaneous pressure-flow studies provides unique and valuable physiologic and diagnostic information. To provide a comprehensive view of the role of upper tract urodynamics in the evaluation of hydronephrosis, this chapter discusses relevant biomechanical principles, pathophysiology of renal obstruction, the evolving understanding of a variety of urodynamic parameters, and the relative advantages and limitations of upper tract urodynamics, comparing percutaneous pressure-flow studies with other commonly used diagnostic tools.

BIOMECHANICAL PRINCIPLES

In any biologic fluid conduit system, the resistance of the conduit is directly proportional to pressure divided by flow (resistance ∝ pressure/flow), a modification of the Poiseuille-Hagen law, which was originally applied to the flow of newtonian fluids through rigid tubes.[1] Based on this principle, both pressure and flow must be taken into account simultaneously to derive a measurement of resistance within the conduit. Unlike other diagnostic modalities, pressure-flow studies are unique in having both the pressure within the collecting system and the rate of fluid flow taken into account simultaneously. Pressure-flow studies therefore provide the basis for deriving a true measure of the resistance of the collecting system, which is ultimately the fundamental source of pathology in hydronephrosis. However, one must be aware of an important caveat: because the urinary tract is not composed of rigid tubes, the compliance of the tissue must be taken into account, especially when the degree of dilatation is extensive.

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*In memory of Leo Fung, a great friend and a dedicated surgeon-scientist, whose investigative work as a fellow at the Hospital for Sick Children in Toronto provided the data upon which this chapter is based.

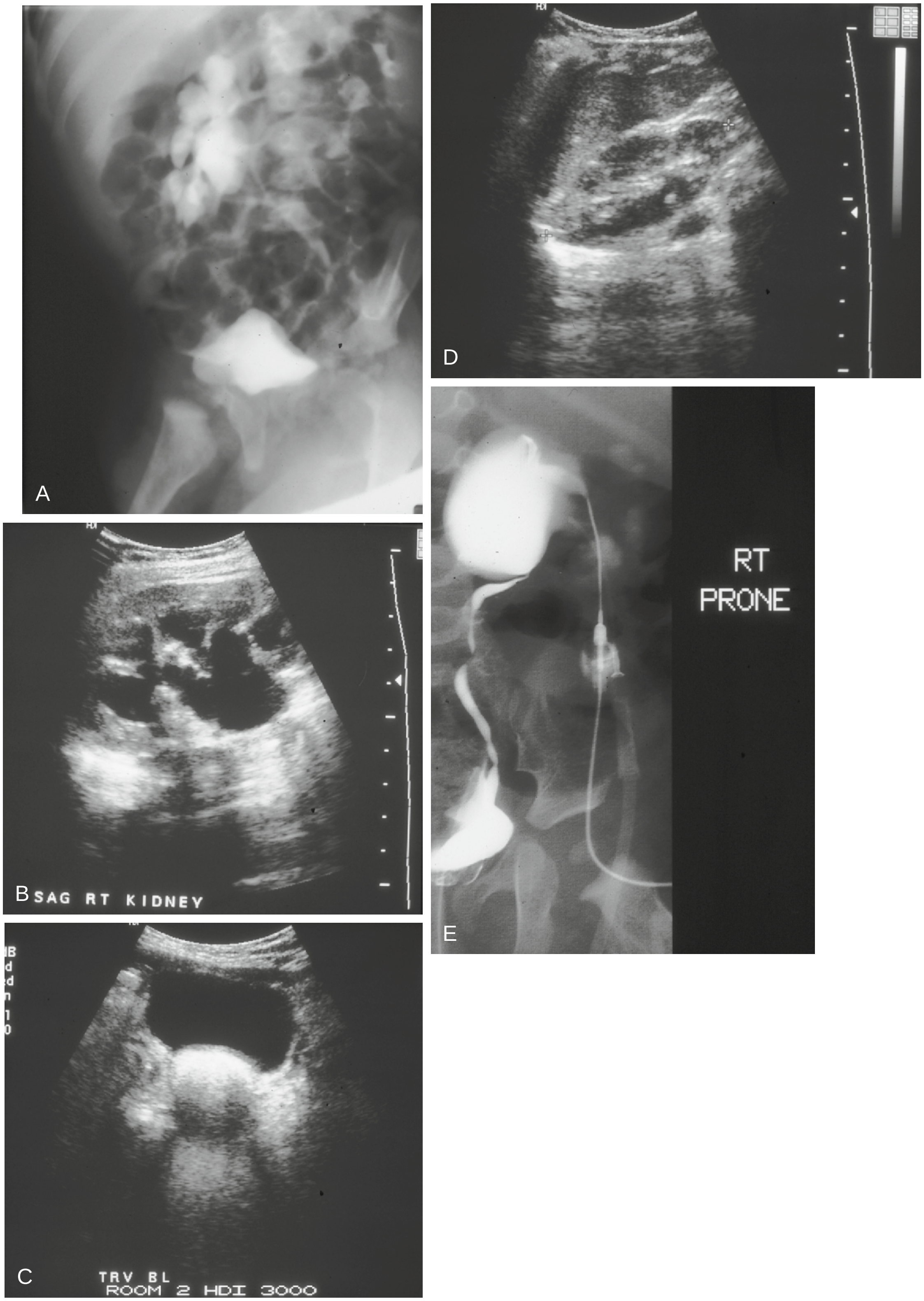

Figure 10-1 Intravenous pyelogram **(A)** and ultrasonogram **(B)** of a 9-month-old boy show right hydronephrosis. There is no ureteral dilatation **(C),** and the left kidney is normal **(D)** by ultrasonography. The patient was further evaluated using a percutaneous pressure-flow study, in which a percutaneous nephrostomy needle was inserted with the patient in the prone position, and antegrade contrast agent infusion **(E)** demonstrated excellent anatomic detail of the right collecting system compatible with ureteropelvic junction obstruction.

Based on the relationship of resistance (being directly proportional to pressure divided by flow), an unobstructed collecting system with normal resistance would maintain a normal intraluminal pressure, able to tolerate any rate of urine output provided that it remains within a physiologic range. Conversely, a hydronephrotic collecting system with an abnormally increased resistance to urine flow would be associated with alterations in its pressure-flow relationship. An increase in resistance would manifest as an elevation in intraluminal pressure at a given flow rate or as a decrease in the rate of urine flow achievable at any given intraluminal pressure. Because intraluminal pressure is technically simpler to determine compared with the selective measurement of urine output from one of two kidneys, current diagnostic pressure-flow studies generally standardize the rate of flow through the collecting system while the intraluminal pressure is continuously monitored. An excessive increase in intraluminal pressure proximal to the suspected site of obstruction subsequent to the flow challenge presented to the collecting system is then used as an indicator of an increased resistance to flow.

In setting up a pressure-flow study, three major considerations determine whether the results obtained will be physiologically meaningful: (1) How should the access be established for the monitoring of collecting system pressure? (2) How should the pressure alterations within the collecting system be interpreted? and (3) How should the rate of flow within the collecting system be generated or maintained during a pressure-flow study? We shall explore these issues in turn, discussing, first, the nephrostomy access; second, the threshold for normal renal pelvic pressure (RPP); and third, the optimal flow challenge to the collecting system.

Other important biomechanical considerations include the differences between a living active ureter and a passive conduit, the compliance of the collecting system, and the dynamic nature of the site of obstruction. The effects of a living ureter with active peristaltic action are addressed as we discuss how best to handle the pressure gradient between RPP and bladder pressure. The effects of compliance are illustrated in performing pressure-flow studies for ureteropelvic junction (UPJ) obstruction as opposed to UVJ obstructions, and the effects of the dynamic nature of the site of obstruction are addressed as we discuss the entity of intermittent obstructions.

PATHOPHYSIOLOGY

A clear understanding of the compensatory changes that occur in response to congenital renal obstruction is critical for the correct interpretation of diagnostic information and to establish a sound management plan. Whereas the majority of experimental work on obstruction of the urinary tract has focused on acute obstruction in mature adult animal models, it is now increasingly apparent that congenital pediatric hydronephrosis behaves much differently than obstruction in the adult kidneys. First of all, the physiologic profile of congenital hydronephrosis lacks the dramatic swings in renal blood flow, glomerular filtration rate (GFR), and RPP seen in acute obstruction and can even be practically indistinguishable from that of a normal kidney. These differences are important in the interpretation of the significance of a positive diuresis pressure-flow study. Second, congenital hydronephrosis has a profound influence on the development of the fetal and infant kidney that is dramatically different from what is seen in the adult kidney.

Renal Blood Flow, Glomerular Filtration Rate, and Renal Pelvic Pressure

Acute ureteral obstruction has been demonstrated to have a classic triphasic response in renal blood flow and RPP (Fig. 10-2).[2] The first phase immediately following acute ureteral obstruction is characterized by an increase in both renal blood flow and RPP lasting 1 to 1.5 hours. The second phase consists of a decrease in renal blood flow but a continuing rise in RPP up to about 5 hours. During the third phase, renal blood flow continues to decrease and RPP also progressively declines. Thereafter, in subacute and chronic ureteral obstruction, renal blood flow remains decreased and RPP progressively declines back to a normal level. GFR alterations essentially mirror the changes in renal blood flow.

In the extensive experimental literature studying acute renal obstruction, elevation in RPP has uniformly been found to be one of the first physical changes. Renal blood flow and GFR changes that are observed after acute renal obstruction are seen only if elevation in RPP was initially present. Therefore, it appears that elevation in RPP constitutes the initial physical stimulus that triggers the subsequent cascade of events in compensatory response to renal obstruction.

After an increase in RPP, many of the subsequent alterations observed in acute renal obstruction are attributable to changes in afferent and efferent arteriolar tone. These changes were initially ascribed to local physical interactions, but they have since been shown by an extensive literature to be secondary to a whole host of biochemical mediators. A comprehensive review was given by Gulmi and colleagues[3] on the many molecular mediators implicated, including the arachidonic acid metabolites (eicosanoids), cyclooxygenase pathway metabolites (prostaglandins or prostanoids), the renin-angiotensin system, atrial natriuretic peptide, nitric oxide, endothelin, platelet-activating factor, clusterin, and transforming growth factor-β. The kidney first undergoes preglomerular vasodilatation, then postglomerular vasoconstriction, and finally preglomerular vasoconstriction.[3]

As the kidney passes from acute obstruction to the chronic phase, preglomerular vasoconstriction persists along with the attendant decrease in renal blood flow. This decrease in blood flow results in a parallel sustained decrease in GFR. The combination of these events in turn leads to a reduction in the initially elevated RPP, returning it to a normal range. An exception to the rule is seen in acute bilateral complete ureteral obstruction, in which the preglomerular vascular tone is in a persistently dilated state, contrary to the preglomerular vasoconstriction seen in unilateral obstruction.[3] As a result, RPP remains elevated in bilateral acute obstruction at times when a reduction would already have been seen in unilateral obstruction.[4] This phenomenon is not fully understood, but it is probably of little relevance to the present discussion, because acute complete bilateral renal obstruction is not encountered as part of the usual clinical spectrum of pediatric hydronephrosis.

In analyzing the relationships among the various physiologic changes that occur in acute renal obstruction, elevation in RPP appears to be the initial physical stimulus that triggers the compensatory cascade. Changes in renal blood flow then act as the key effector mechanism of subsequent compensatory changes, leading to secondary changes in GFR. These compensatory changes then come full circle as alterations in renal blood flow and GFR have a direct effect on RPP. By the time renal blood flow and GFR have declined sufficiently for RPP to decline to the normal range, the initial alterations triggered by the elevation in RPP have abated, and the compensatory changes have established a new equilibrium. Whereas the

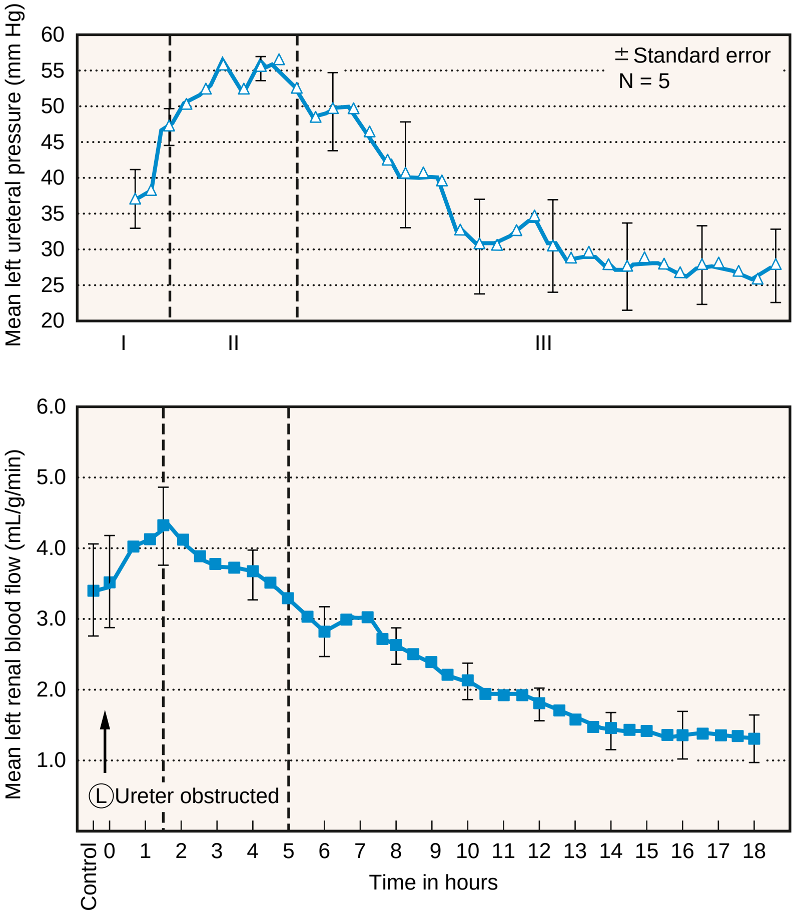

Figure 10-2 The triphasic relationship between ipsilateral renal blood flow and left ureteral pressure during 18 hours of left-sided occlusion. The three phases are designated by Roman numerals and divided by *vertical dashed lines.* In phase I, renal blood flow and ureteral pressure rise together. In phase II, the left renal blood flow begins to decline, whereas ureteral pressure remains elevated and, in fact, continues to rise. Phase III shows the left-sided renal blood flow and ureteral pressure declining together. (From Moody TE, Vaughan ED Jr, Gillenwater JY. Relationship between renal blood flow and ureteral pressure during 18 hours of total unilateral ureteral occlusion. *Invest Urol.* 1975;13:246-251.)

evidence supporting this cascade of events is derived primarily from experimental models of acute renal obstruction, it appears that these events are also at work, at least in part, in congenital hydronephrosis.

In contrast to acute renal obstruction, congenital hydronephrosis is consistently found to have normal RPP at baseline hydration levels (Fig. 10-3).[5] Because of the complex interactions among stimuli for renal growth and effects on renal injury, kidneys with congenital hydronephrosis can have normal, decreased, or even increased renal blood flow compared with normal kidneys.[6,7] Therefore, a congenitally hydronephrotic kidney with physiologically significant obstruction can maintain physiologic parameters difficult to distinguish from those of a normal kidney at baseline conditions. In order to develop strategies that will be effective in accurately detecting those hydronephrotic kidneys that have physiologically significant obstruction, it is important to identify pathophysiologic features that distinguish the congenital hydronephrotic kidney with significant obstruction from the normal kidney.

The mode of renal injury in obstructed kidneys may provide an important clue for formulating effective diagnostic strategies. Although there is much evidence showing that persistently elevated RPP is linked to irreversible renal injury,[8,9] there is as yet no conclusive evidence that the direct pressure effect is harmful to renal cellular elements. On the other hand, the obstructed kidney with decreased renal blood flow as part of the compensatory response has been shown to be associated with an upregulation in vascular endothelial growth factor, a molecular marker for physiologically significant ischemia at the cellular level.[9] Therefore, the mode of injury for the obstructed kidney appears not to result directly from the pressure effects but is instead ischemic in nature, resulting from the compensatory response in renal blood flow reduction. From a teleologic point of view, it is unclear what protective advantage is provided to someone with an obstructed kidney by these compensatory events. Nevertheless, these compensatory responses remain activated until the RPP is brought back to normal, even at the expense of decreased renal blood flow, decreased GFR, and, ultimately, renal cellular ischemia.

Although there is little information on exactly how the congenitally hydronephrotic kidney consistently maintains normal RPP at the baseline hydration state, it seems reasonable to presume that the response of a congenitally hydronephrotic kidney to obstruction shares features with that of the acutely obstructed kidney. In this view, RPP would be maintained at the expense of compensatory changes in renal blood flow and GFR, similar to what is seen in the acute obstruction models. This postulate is supported by the changes in RPP observed in congenitally hydronephrotic kidneys in response to diuresis, when compared with normal kidneys.

Whereas it is our experience in a pig model that it is practically impossible to induce an elevation in RPP in normal collecting systems by instituting a forced diuresis, in children with congenital hydronephrosis RPP rises from the normal level of less than 10 cm H_2O to as high as 63 cm H_2O after a furosemide-induced diuresis (see Fig. 10-3).[5] This pattern was also observed when rats with congenital hydronephrosis were compared with normal controls.[10] Therefore, it appears that RPP is normal in a nonhydronephrotic kidney because the normal collecting system has a huge reserve capacity

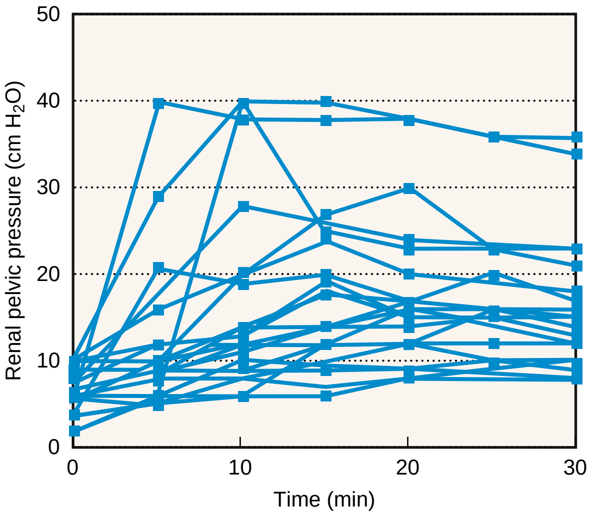

Figure 10-3 Composite graph of data from a representative group of patients with hydronephrosis undergoing diuresis pressure-flow studies, in which renal pelvic pressure (RPP) is plotted against time. RPP at time 0 represents baseline pressure. Intravenous furosemide, 1 mg/kg up to a maximum of 10 mg, was given at time 0, and RPP was monitored for 30 minutes. The furosemide-induced diuresis constituted the sole form of fluid challenge, and no infusion of fluid took place during these studies. In our experience studying more than 55 hydronephrotic kidneys to date (data not all plotted on this graph in order to maintain clarity), it has been consistently observed that the prediuresis baseline RPPs remain relatively low and do not exceed 10 cm H_2O. The highest RPP that we have recorded after furosemide-induced diuresis was 63 cm H_2O, which was observed in a patient with ureteropelvic junction (UPJ) obstruction, and no contrast material was seen draining across the UPJ throughout the entire pressure-flow study.

for handling additional urine flow. In contrast, congenitally hydronephrotic kidneys with significant obstruction are able to maintain normal RPP because they have undergone compensatory changes in renal blood flow and GFR to achieve a new equilibrium, and there is little or no reserve for handling an induced diuresis. This line of reasoning forms the pathophysiologic basis for the diuresis pressure-flow study described later (see Diagnosis), whereby significantly obstructed kidneys are distinguished from nonobstructed kidneys by their response to diuresis. Nonobstructed kidneys maintain normal RPP after the induction of diuresis, but diuresis perturbs the obstructed kidney from its compensated state of equilibrium, and its initially compensated normal RPP becomes elevated.

Developmental Influence on the Fetal Kidney

The degree to which a fetal kidney develops when under the influence of obstruction appears to depend on the timing of the onset of obstruction as well as on the degree of obstruction. Whereas later onset and incomplete obstruction in utero lead to hydronephrosis with a varying degree of functional renal development, early and complete obstruction results in irreversible renal dysplasia with no functional potential in the dysplastic renal elements.[11,12] In the spectrum between normal and obvious hydronephrosis, there are also instances in which the dilatation in the collecting system can be considered transient or physiologic, with brief periods of distention seen as the bladder fills during the increased diuresis of the third trimester. No lasting effects on such kidneys are observed postnatally.[13]

It has long been recognized that congenital hydronephrosis represents a spectrum of conditions, with the functional potential of the hydronephrotic kidney ranging from complete nonfunction, as in the case of total dysplasia, to entirely normal renal function indistinguishable from that in normal kidneys. More interestingly, the possibility has been raised that congenital hydronephrosis may result in a kidney that functions at a level in excess of the normally expected range.[6] This phenomenon, termed *supranormal differential renal function*, describes a unilaterally hydronephrotic kidney that has a significantly higher differential renal function than the normal contralateral mate. The significance of these findings remains unclear.

Several clinical series have evaluated the phenomenon of supranormal differential renal function. Fung and coworkers[7] studied 16 patients who had a differential renal function of 53% or higher in the unilateral hydronephrotic kidney. Whereas the supranormal differential renal function phenomenon appeared convincing based on the findings of diethylenetriamine penta-acetic acid (DTPA) nuclear renography (mean, 58.3%; range, 53% to 66%), the differential renal function observed was less dramatic when these same patients were evaluated using dimercaptosuccinic acid (DMSA) nuclear renography (mean, 51.1%; range, 42% to 57%). The results from the DMSA renal scans were not significantly different from the intuitively expected normal differential function of 50%. Therefore, the phenomenon of supranormal differential function appeared to be an artifact specific to DTPA nuclear renal scans, presumably secondary to the accumulation of background activity in the region of the dilated renal pelvis and calyces which prevents an accurate assessment of the true differential renal function. This confounding variable would not apply to DMSA renal scans, in which background activity is less of an issue.

Contrary to these findings, Capolicchio and associates[14] reported a similar study on 15 patients, defining supranormal differential renal function as greater than 55%. The mean differential renal function in these 15 patients was 55% ± 4% based on DTPA renal scan (range, 46% to 61%) and 55% ± 3% based on DMSA renal scan (range, 51% to 62%). The authors concluded that there was no significant difference between the differential renal function assessments performed by DTPA and by DMSA renal scans and that supranormal differential renal function was a real phenomenon. A report by Kim and colleagues[15] concluded, similarly, that supranormal differential renal function was a real phenomenon. Fourteen patients had differential renal function assessments by DTPA renal scan and were further assessed by split urinary collection and split creatinine clearance measurements. Supranormal differential renal function was confirmed by split creatinine clearance in 2 patients and was shown to be a spurious finding in 1. DTPA renal scans had a tendency to overestimate differential renal function when compared with split creatinine clearance, especially for those kidneys that had a significantly reduced renal function.

From these clinical series, it appears that supranormal differential renal function is a real phenomenon in unilateral hydronephrosis. It also seems that DTPA renal scans have a tendency to overestimate differential renal function, compared with DMSA renal scans or split urinary creatinine clearance measurements. Experimental work in fetal sheep by Peters and Fung and their associates[16,17] provided further evidence to support the validity of supranormal differential renal function in unilateral hydronephrosis. Partial unilateral ureteral obstruction was observed to produce hydronephrotic kidneys that had a larger renal weight than their contralateral normal mate or age-matched controls. DNA, RNA, and protein contents were analyzed to distinguish hyperplasia from hypertrophy. An increase in DNA content signified a hyperplastic response (i.e., the net number of cells present was increased). On the other hand, an increase in the ratio of RNA to DNA or protein to DNA signified that the cells had increased in size and therefore were hypertrophic in nature. In these unilaterally partially obstructed fetal sheep kidneys, it was found that the increase in weight was secondary to hyperplasia, and there was no evidence of hypertrophy. These findings are in keeping with the concept of supranormal differential renal function in unilateral congenital hydronephrosis: there is a true increase in functional capacity in these hydronephrotic kidneys, because they have developed to a larger size than their contralateral normal mate or age-matched controls, secondary to a hyperplastic response. Furthermore, supranormal renal development was seen only in relatively mild partial unilateral ureteral obstruction.[17] In more severe obstruction, the hydronephrotic kidneys were observed to have a significantly decreased renal weight.[16,18]

Summarizing the current concepts of the response of the fetal kidney to renal obstruction in utero, early onset and severe renal obstruction result in predominantly renal dysplasia with no significant functional potential in the dysplastic elements. Later onset and partial obstruction result in hydronephrotic kidneys with varying degrees of functional potential. Whereas partial obstruction can certainly lead to hydronephrotic kidneys that have a diminished renal weight and decreased functional capacity, in certain instances milder forms of partial obstruction can also act as a stimulus for the hydronephrotic kidney to undergo hyperplasia, becoming larger than normal secondary to the development of an increased number of cellular elements. These larger-than-normal hyperplastic unilateral hydronephrotic kidneys seen in experimental models likely correlate with supranormal differential renal function observed in patients, in which a unilateral hydronephrotic kidney possesses functional potential greater than that of its contralateral normal mate.

In the assessment of postnatal differential renal function, it is important for the clinician to be aware that the baseline differential renal function for hydronephrotic kidneys may not be the intuitively expected 50% but has been reported to be as high as 66%. Accordingly, indications for more invasive testing or for surgical correction of obstruction should not be based exclusively on an arbitrarily chosen differential renal function. Rather, they should take into account the appearance of the collecting system and parenchyma in addition to the changes in differential function on serial evaluations.

PERCUTANEOUS PRESSURE-FLOW STUDIES

Imaging modalities are highly effective in the detection of dilatation of the collecting system and in the delineation of the exact site of anatomic obstruction. However, whereas some hydronephrotic kidneys undergo progressive functional deterioration, others remain stable or even undergo spontaneous improvement. In order to determine the appropriate course of management, it is therefore imperative to accurately detect those hydronephrotic kidneys that are at risk for progressive injury, separating kidneys with significant obstruction from those that merely have innocuous dilatation of the collecting system.

In order to clearly delineate the strengths and limitations of percutaneous pressure-flow studies, it is necessary to have a working definition of what constitutes significant obstruction. Implicit in the preceding discussion on the pathophysiology of congenital hydronephrosis, *physiologically significant obstruction* can be defined as an impediment in urine transport that leads to compensatory changes in physiologic renal parameters, including but not limited to RPP, renal blood flow, and GFR. However, a kidney identified as having physiologically significant obstruction may not necessarily suffer from functionally significant sequelae. Therefore, *functionally significant obstruction* can be separately defined as an impediment in urine transport that, if left untreated, will ultimately result in the kidney's having less than the full functional potential it would otherwise possess. The management of hydronephrosis continues to be highly controversial, to a large extent because it remains unclear whether physiologically significant obstruction necessarily leads to functionally significant obstruction. Nevertheless, with these working definitions in mind, percutaneous pressure-flow studies are discussed according to their ability to delineate the anatomic site of obstruction, to detect physiologically significant obstruction, and to diagnose functionally significant obstruction. Our current pressure-flow study protocol is summarized in Table 10-1. Key components of this protocol are discussed in the following sections.

Nephrostomy Access

The invasive nature of pressure-flow studies stems from the need to obtain direct access to the lumen of the collecting system in order to provide a means to measure the fluid pressure within the system. In spite of the astounding technological advances occurring in the field of biomedical sciences, there is as yet no truly noninvasive way to measure fluid pressure. Fluid pressure can be measured by one of two methods: (1) by direct access to a fluid column that comes into continuous contact with the site of interest, as in the typical pressure transducer used in urodynamics, arterial line pressure, central venous pressure, cerebrospinal fluid, and other similar fluid pressure monitoring systems, or (2) by applying circumferential compression of variable pressure to the structure of interest—the pressure at which flow resumes within the structure of interest is equivalent to the fluid pressure within (the same principle that is behind blood pressure measurements using a blood pressure cuff). This second method is not applicable to pressure-flow studies, because circumferential compression of the collecting system cannot be easily achieved. Therefore, pressure-flow studies of the upper urinary tract remain invasive in nature, requiring direct access to the lumen proximal to the suspected site of obstruction. For pragmatic reasons, this access is generally established via percutaneous hollow needles or angiocatheters or by an indwelling nephrostomy tube.

For technical reasons that are further addressed in the discussions of individualized infusion pressure-flow studies, it is advantageous to have two separate nephrostomy accesses to the renal pelvis, one for pressure monitoring and one for fluid infusion. For elective pressure-flow studies, insertion of two 22-gauge 2-inch angiocatheters under ultrasonographic guidance and fluoroscopic monitoring by our pediatric interventional radiologist has been found to be effective and safe. For older children, the 2-inch angiocatheters may be too short. In such cases, 22-gauge spinal needles have been found to be effective. Whereas percutaneous nephrostomy accesses can be safely established under local anesthesia in adults, we routinely employ general anesthesia for such procedures in children. Bilateral percutaneous pressure-flow studies can also be performed safely simultaneously, with two nephrostomy accesses established for each side (Fig. 10-4).

Threshold for Normal Renal Pelvic Pressure

Regardless of which form of pressure-flow study is used, meaningful interpretation of the results depends on the fundamental question of what constitutes the upper limit of normal

Table 10-1 Current Pressure-Flow Study Protocol at the University of Massachusetts Memorial Medical Center, Worcester, and the Hospital for Sick Children, Toronto

Patient is placed under general anesthesia with endotracheal intubation.

With IV access established, antibiotic prophylaxis is given using 25 mg/kg of IV cephazolin up to a maximum of 1 g, provided that there is no history of allergic reaction, and hydration is begun with a minimum of 15 mL/kg of a crystalloid solution.

With the patient in the supine position, the bladder catheter is inserted, using the largest-caliber catheter that the patient can accept.

To facilitate placement of percutaneous nephrostomy needles, the bladder catheter may be plugged off at this stage to keep the bladder full and maximize renal pelvic dilatation.

Patient is turned to prone position, and ultrasonographic examination is carried out to plan for nephrostomy access.

Patient is sterilely prepared and draped. Under ultrasonographic guidance, two 22-gauge 2-inch angiocatheters (or other suitable catheters or needles) are inserted percutaneously into the renal pelvis to be examined.

Bilateral percutaneous pressure-flow studies can be safely performed simultaneously, with two nephrostomy accesses per side.

The bladder is emptied, and the catheter is connected to gravity drainage.

To verify placement of the nephrostomy access and to establish a means to monitor the progress of urine flow, radiographic contrast material is injected into the renal pelvis via nephrostomy access. To preserve the baseline RPP dynamics, an equal volume of urine is first aspirated out before the contrast material is injected.

One of the nephrostomy accesses is capped off, and the other is connected to a pressure transducer with no flow going through the nephrostomy.

The pressure transducer line is zeroed externally to the same level as the tip of the nephrostomy access within the renal pelvis. When it is connected to the nephrostomy access, the initial pressure reading represents the baseline renal pelvis pressure.

Furosemide (1 mg/kg IV, up to a maximum of 10 mg) is given to begin the *diuresis pressure-flow study* component.

RPP is continuously monitored for 30 min. Urine output is measured every 5 min to verify satisfactory overall response to IV hydration and furosemide. The peak RPP observed in this period determines whether the diuresis pressure-flow study is positive (peak RPP >14 cm H_2O) for significant obstruction.

During this 30-min interval, fluoroscopy is used intermittently. The RPP at which radiographic contrast material is first seen distal to the suspected level of obstruction constitutes the *ureteral opening pressure*.

If the diuresis pressure-flow study component is strongly positive for significant obstruction (peak RPP markedly greater than 14 cm H_2O), an antegrade nephrostogram is performed to obtain anatomic details necessary for guiding surgical repair, and the percutaneous pressure-flow study is concluded at this point.

If the diuresis pressure-flow study component peak RPP is close to or less than 14 cm H_2O, the *individualized infusion pressure-flow study* is performed next. The other capped-off nephrostomy access is connected to an infusion pump, infusing a radiographic contrast solution. The rate of infusion is individually calculated based on the patient's age, weight, and height (see Table 10-2) or on the GFR of the kidney being tested, if known.

If the resulting RPP is positive for significant obstruction (>14 cm H_2O), an antegrade nephrostogram is performed to obtain anatomic details necessary for guiding surgical repair, and the percutaneous pressure-flow study is concluded at this point.

If the resulting RPP pressure is negative for significant obstruction (≤14 cm H_2O), a supraphysiologic rate of infusion is then used (150-200% of the individualized infusion rate).

Note: Regardless of whether the RPP pressure rises above 14 cm H_2O at this point, the pressure-flow study is still considered negative for significant obstruction. The supraphysiologic rate of infusion is used as a measure of the *reserve capability* of the collecting system to handle additional urine flow.

If a lower tract abnormality that causes excessively high intravesical pressure coexists with the upper tract obstructive site, an initially negative study for significant obstruction (diuresis pressure-flow study or individualized infusion pressure-flow study) can be further challenged with the bladder filled to the peak naturally occurring intravesical pressure. This is performed by connecting an IV solution drip to the bladder catheter and raising the drip chamber to a level that is the same height (in centimeters) as the peak intravesical pressure (in centimeters of water). The desired intravesical pressure being simulated is reached when the drip slows to intermittent drops or stops. The peak RPP recorded in this setting represents a combined effect of both the upper tract obstructive site and the lower tract anomaly on their corresponding upper tract urodynamics *(combined upper and lower tract urodynamics)*.

Once all necessary urodynamic measurements have been completed, an *antegrade nephrostogram* is performed to obtain anatomic details necessary for guiding surgical repair. The renal pelvis is aspirated empty, and the nephrostomy accesses are removed. The patient is turned back to the supine position and awakened from anesthesia. The bladder catheter is removed once significant gross hematuria has been ruled out and the patient is sufficiently awake to void.

All patients who have percutaneous pressure-flow studies positive for significant obstruction are prescribed oral antibiotic prophylaxis until successful surgical repairs have been achieved.

GFR, glomerular filtration rate: IV, intravenous; RPP, renal pelvic pressure.

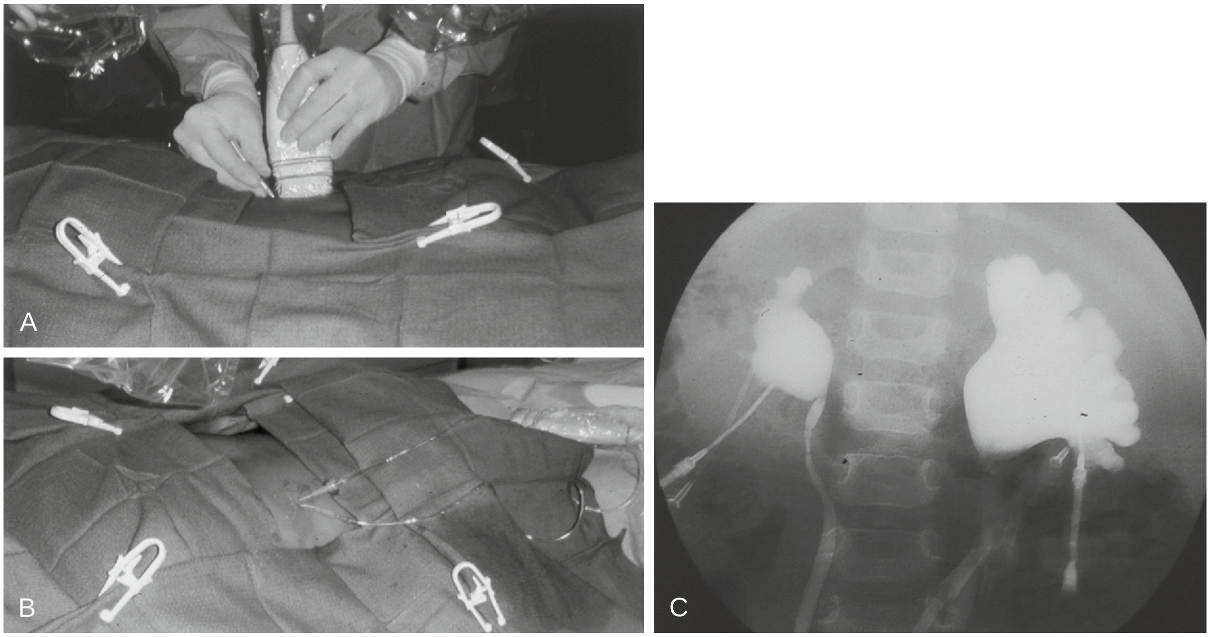

Figure 10-4 **A,** With the patient in the prone position and under general anesthesia, two angiocatheters or needles are inserted into the renal pelvis with ultrasonographic guidance. **B,** With the nephrostomy accesses in place, antegrade infusion of contrast medium verifies satisfactory nephrostomy placement. **C,** Bilateral percutaneous pressure-flow studies can also be performed safely simultaneously, with two nephrostomy accesses inserted in each side. In this 1½-year-old boy, the pressure-flow study indicated significant ureteropelvic junction obstruction bilaterally. He is currently well after successful staged pyeloplasties.

collecting system pressure. There are a number of studies, both experimental and clinical, that help answer this question.

In the rat model, it was found that the proximal tubular, intratubular, and peritubular capillary pressures remain constant until the collecting system pressure exceeds the normal tubular pressure. In this context, the normal proximal tubular pressure was established to be 14.1 ± 0.5 cm H_2O in the rat.[19] Human data have been shown to be in keeping with these results. In the human, intrarenal arterial resistance increases acutely once the RPP rises to greater than 14 cm H_2O.[20] Furthermore, Fichtner and coworkers[10] showed, in the congenital hydronephrosis rat model, that the hydronephrotic kidneys with an empty bladder had a mean RPP of 14.1 ± 1.6 cm H_2O under very high urine output, and the mean RPP increased further if the bladder was filled. Conversely, the normal control kidneys with the bladder empty resulted in a mean RPP well below 14 cm H_2O, even with very high urine output; additionally, with the bladders filled to capacity, the highest mean RPP recorded was only 13.2 ± 1.6 cm H_2O. These lines of evidence all indicate that 14 cm H_2O is the upper limit of normal RPP, above which undesirable physiologic changes begin to occur.

Whereas these results indicate that RPPs greater than 14 cm H_2O produce undesirable physiologic changes, additional evidence indicates that elevation in RPP leads to acute and irreversible renal injury within a relatively short time span (<24 hours). In a porcine model in which RPP was kept constantly elevated at between 20 and 40 cm H_2O, the urinary level of *N*-acetyl-β-D-glucosaminidase was found to be elevated, indicative of acute renal tubular cell membrane disruption.[21] Similar experiments also demonstrated that elevation in RPP led to acute onset of apoptotic cell death, suggestive of a component of irreversible injury.[8] Such acute tubular disruption and apoptotic cell death were further found to be associated with decreased renal blood flow and alterations in vascular endothelial growth factor messenger RNA levels, providing evidence that decreased perfusion and tissue hypoxia play an important role in kidneys with elevated RPPs.[9] These indications of renal injury were significantly greater in the experimental group with RPP ranging from 20 to 40 cm H_2O, compared with the control animals with RPP of 10 cm H_2O or less.

Based on these results, the threshold for physiologically safe RPP seems to lie somewhere between 10 and 20 cm H_2O. Even though these experiments did not pinpoint the exact threshold for normal RPP (i.e., the level above which renal injury occurs), the data are in keeping with 14 cm H_2O as the upper limit of normal RPP as established in rat and human studies. From these lines of evidence, we advocate use of 14 cm H_2O as the cutoff for physiologically safe RPP, with higher levels considered abnormal and expected to result in undesirable physiologic changes and renal injury.

Optimal Flow Challenge to the Collecting System

Because urine output can vary tremendously under normal physiologic conditions, the collecting system is expected to be able to handle a large range of urine flow rates within physiologic limits. Based on the modified Poiseuille-Hagen law described earlier (i.e., the resistance of a conduit is directly proportional to pressure divided by flow), an "obstructed" collecting system with abnormally high resistance would be especially prone to development of elevated pressures when the flow rate is high. In other words, a severely obstructed system with grossly increased resistance will develop elevated pressures with even relatively modest flow challenges. A partially obstructed system with marginally increased resistance to flow may be able to handle lower flow rates but will develop high pressures when the flow rate increases. A normal collecting system will maintain normal pressures throughout the entire range of physiologic flow rates. However, even normal collecting systems may become overwhelmed by a high flow challenge that exceeds physiologic limits, resulting in an elevation in pressure within the collecting system.

In selecting a flow rate that would optimally challenge the collecting system, one should consider the maximum urine output that the kidney in question is capable of generating under normal physiologic conditions. Use of the maximum urine output possible for the kidney studied ensures that the collecting system is maximally challenged to uncover even more subtle forms of obstruction, whereas the flow challenge itself remains within physiologic confines, so that artificially elevated RPPs are avoided. The maximum physiologic urine output that a kidney can generate can be determined with the use of a calculated estimate *(individualized infusion pressure-flow study)* or can be simulated pharmacologically *(diuresis pressure-flow study)*.

Individualized Infusion Pressure-Flow Study

Much of the pioneering work in infusion pressure-flow studies can be attributed to Whitaker.[22] In this form of pressure-flow study, commonly referred to as the *Whitaker test*, the collecting system is challenged with an externally generated infusion at a known flow rate via a nephrostomy access. At this infusion rate, if the collecting system pressure remains within an acceptable range (0 to 12 cm H_2O in Whitaker's description), the study is interpreted as being negative and as showing no significant obstruction. Conversely, if the collecting system pressure becomes significantly elevated (>20 cm H_2O in Whitaker's description), the study is interpreted as positive and indicative of significant obstruction. Whitaker advocated use of a standard infusion rate of 10 mL/min, with 5- or 2-mL/min infusion rates substituted for smaller children; a rate of 15 mL/min could be used if a more stringent flow challenge were deemed necessary. Although these concepts are sound in principle, recognizing the need to tailor the infusion rate to patients of different ages and body sizes, there was little information at that time regarding which infusion rate should be used for what age and body size. Further work in this area was undertaken by Fung and associates[5] in an attempt to provide more specific guidelines, so that the infusion rate used would provide physiologically meaningful results.

Adhering to the principle that the flow rate selected should reflect the maximum urine output that the kidney in question is capable of generating under normal physiologic conditions, a method for calculating maximum physiologic urine output was devised. Three patient parameters form the basis for the calculated estimate of the patient's maximum physiologic urine output: (1) the body surface area, (2) the age-adjusted 90th percentile GFR, and (3) the maximum percentage of the GFR that one can physiologically diurese.

The surface area (m^2) can be obtained from a population nomogram, based on the patient's height and weight.[23] The 90th percentile GFR (mL/min/1.73 m^2) for the patient's age can also be obtained from a population nomogram (Fig. 10-5).[24] This latter value is then adjusted for the patient's size to obtain the total GFR:

Calculated total GFR (mL/min) = Age-adjusted GFR × Body surface area ÷ 1.73

Because the renal tubules proximal to the segment sensitive to antidiuretic hormone reclaim about 80% of the water in the glomerular ultrafiltrate, the maximum physiologic diuresis cannot exceed approximately 20% of the GFR under nonpathologic conditions, even in the complete absence of antidiuretic hormone.[25] The calculation can be summarized as follows:

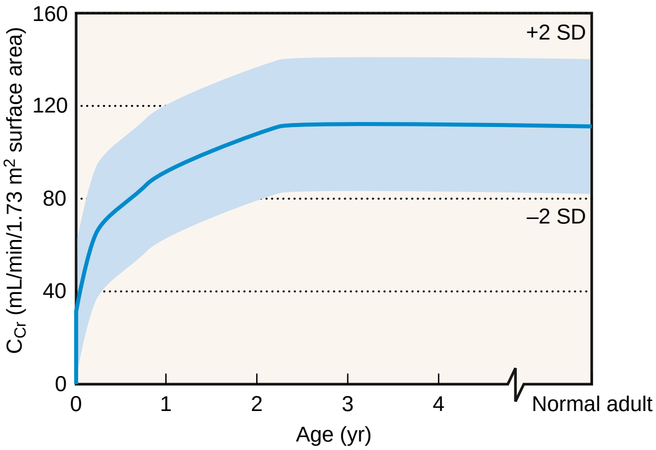

Figure 10-5 Age-adjusted glomerular filtration rate (in milliliters per minute per 1.73 m^2 surface area) nomogram. C_{Cr}, creatinine clearance; SD, standard deviation. (From McCrory WW. *Developmental Nephrology*. Cambridge, MA: Harvard University Press; 1972.)

Maximum physiologic output per kidney (mL/min) = Calculated total GFR × 20% ÷ Number of kidneys

Because the pressure-flow study is applied to one kidney at a time, the flow rate employed is based on the maximum physiologic urine output per kidney; hence, the correction factor, "Number of kidneys." For patients who have a solitary kidney, compensatory hypertrophy or hyperplasia needs to be taken into account. The formula is directly applicable only if the GFR of the solitary kidney has compensated to a level similar to the population's normal total GFR.

For a patient whose total GFR and differential renal function are known, the maximum physiologic urine output can be derived directly from those results. Maximum physiologic urine output for the kidney of interest would then be 20% of the measured total GFR (mL/min) multiplied by the differential renal function for that kidney (percent):

Maximum physiologic output per kidney (mL/min) = Measured total GFR × 20% × Differential renal function

When these calculations were performed for patients of various ages and body sizes, the appropriate infusion rate corresponding to their respective maximum physiologic urine output per kidney ranged from 0.85 mL/min (appropriate for a small, 4-week-old infant) to 16.31 mL/min (appropriate for a large, 18-year-old patient). This tremendously wide range underscores the importance of individualizing the infusion rate for each pediatric patient.

When an infusion pressure-flow study is performed, we advocate that the age, height, and weight of the patient be obtained. From these three simple variables, the appropriate infusion rate can be quickly determined by consulting Table 10-2.[5] This individualized infusion rate represents the rate of urine flow that the kidney in question should be able to tolerate if the system were nonobstructive. The infusion pressure-flow study should be performed with the infusion carried out at this individualized rate. A nonobstructive system should maintain a peak RPP of 14 cm H_2O or less, whereas a collecting system with significant obstruction would have a peak RPP of greater than 14 cm H_2O. These modifications from Whitaker's original descriptions form the basis for the *individualized infusion pressure-flow study*.

Table 10-2 **Height, Weight, and Glomerular Filtration Rate (GFR) Values Obtained from Population Nomograms***

Age (Yr)	Height (cm)		Weight (kg)		Surface Area (m^2)		90th Percentile GFR (mL/min/1.73 m^2)	Maximum Physiologic Urine Output per Kidney (mL/min)	
	10th Percentile	90th Percentile	10th Percentile	90th Percentile	10th Percentile	90th Percentile		10th Percentile	90th Percentile
4 wk	50.5	56.5	3.3	4.8	0.210	0.260	70	0.85	1.05
8 wk	53.0	60.0	3.9	5.6	0.225	0.290	80	1.04	1.34
12 wk	55.5	63.0	4.6	6.6	0.250	0.320	90	1.30	1.66
16 wk	58.0	66.0	5.3	7.5	0.275	0.350	98	1.56	1.98
20 wk	60.0	68.0	5.9	8.3	0.295	0.375	105	1.79	2.28
0.5	62.5	71.0	6.6	9.4	0.320	0.405	108	2.00	2.53
0.6	64.5	73.0	7.1	10.0	0.340	0.430	111	2.18	2.76
0.7	66.5	75.0	7.5	10.5	0.355	0.445	114	2.34	2.93
0.8	68.0	76.5	7.8	10.9	0.360	0.460	116	2.41	3.08
0.9	69.5	78.5	8.1	11.3	0.380	0.480	118	2.59	3.27
1	74.0	80.0	8.4	11.7	0.400	0.490	120	2.77	3.40
2	80.0	90.0	10.5	14.5	0.470	0.630	138	3.75	5.03
3	88.0	99.0	12.5	17.0	0.540	0.660	144	4.49	5.49
4	94.5	107.0	13.0	19.0	0.560	0.730	144	4.66	6.08
5	101.0	114.5	14.5	21.5	0.630	0.810	144	5.24	6.74
6	107.0	121.0	17.0	24.5	0.700	0.890	144	5.83	7.41
7	112.0	128.0	19.0	28.0	0.760	0.980	144	6.33	8.16
8	117.5	133.5	21.0	31.0	0.820	1.050	144	6.83	8.74
9	123.0	139.0	23.0	35.0	0.870	1.150	144	7.24	9.57
10	128.0	144.5	25.0	40.0	0.930	1.260	144	7.74	10.49
11	133.5	150.0	27.5	44.5	1.000	1.360	144	8.32	11.32
12	138.5	157.0	30.0	51.0	1.070	1.480	144	8.91	12.32
13	143.5	164.0	32.5	59.5	1.140	1.640	144	9.49	13.65
14	152.0	169.0	39.5	64.5	1.300	1.740	144	10.82	14.48
15	154.0	177.0	47.0	68.0	1.420	1.830	144	11.82	15.23
16	154.5	181.0	48.5	71.5	1.450	1.900	144	12.07	15.82
17	154.5	182.5	48.5	73.5	1.450	1.940	144	12.07	16.15
18	154.5	183.0	49.0	74.5	1.460	1.960	144	12.15	16.31
19	154.5	183.0	49.0	75.0	1.460	1.970	144	12.15	16.40

*The calculated maximum physiologic urine outputs are provided as rough guidelines for determining the individualized pressure-flow study infusion rate. *Note:* The maximum urine output estimates tabulated here are expressed as the infusion rate per kidney, representing half of the total calculated urine output estimate. For patients with a solitary kidney, the infusion rate may need to be increased in proportion to its compensatory increase in GFR.

Constant Pressure Perfusion Study

The threshold of normal RPP of 14 cm H_2O and the optimal flow challenge to the collecting system as established in the individualized infusion pressure-flow study are concepts that are equally applicable to an alternative method in conducting pressure-flow studies, referred to as the *constant-pressure perfusion study*.[26-28] In this procedure, the RPP becomes the variable. In the pressure-flow studies discussed earlier, the rate of fluid challenge is systematically varied while the resulting alterations in RPP are monitored; in the constant-pressure perfusion study, the RPP is systematically varied while the resulting flow across the suspected site of obstruction is measured.

For proponents of the constant-pressure perfusion alternative, the lack of information regarding normal pressure-flow relationships has also been problematic.[26-28] Pending further validation, it would appear logical that the upper limit of normal RPP of 14 cm H_2O should be applicable regardless of the form of pressure-flow study used. Similarly, the optimal flow challenge to the collecting system as calculated in the individualized infusion pressure-flow study (the estimated maximum physiologic urine output) should provide physiologically relevant guidelines as to what amount of urine flow should be anticipated across the suspected site of obstruction.[5] In other words, when the RPP is brought to the physiologically tolerable upper limit (14 cm H_2O), a resultant flow rate that is greater than or equal to the calculated estimate of the maximum physiologic urine output (see Table 10-2) is indicative of efficient urine transport. Conversely, a resultant flow rate less than the calculated estimate of the maximum physiologic urine output indicates that the collecting system is incapable of handling maximal physiologic diuresis without raising the RPP above the upper limit of normal.

When performed using the pressure-flow guidelines as established for the individualized infusion pressure-flow study,[5] the constant-pressure perfusion variation should theoretically generate comparable results. However, we do not employ the constant-pressure perfusion method in the evaluation of our patients, primarily for two reasons. First, the exact measurement of the rate of flow across the suspected site of obstruction is difficult. Measurement of flow by timed (1- to 2-minute) volumes[28] entering the bladder does not provide continuous monitoring that would reflect real-time changes (as one would obtain from conventional RPP monitoring), and it also fails to exclude the urine flow contribution from the contralateral ureter. Second, we have now identified a substitute for external fluid infusion, namely a pharmacologically induced diuresis. As discussed in the next section, this modification both appears to be more physiologic and reveals additional diagnostically important information. Because the constant-pressure perfusion study is conceptually not adaptable to accommodate an induced diuresis, the concept is currently not applicable to our pressure-flow study protocol.

Diuresis Pressure-Flow Study

Despite the use of infusion rates that are as physiologically relevant as possible, the individualized infusion pressure-flow study remains somewhat arbitrary, because it relies on an external infusion pump to provide the flow challenge to the collecting system, instead of a more physiologic form of urine output. For this reason, we explored whether it would be possible to eliminate the need for an external infusion during a pressure-flow study and instead challenge the collecting system with a diuresis induced by the administration of intravenous furosemide. In performing such a *diuresis pressure-flow study*, nephrostomy access and urethral catheterization would be carried out in a manner similar to that of the individualized infusion pressure-flow study. Instead of an external infusion, the patient first receives an intravenous bolus of 15 mL/kg of a crystalloid solution, to ensure adequate hydration, and then 1 mg/kg of intravenous furosemide, up to a maximum of 10 mg. RPP is continuously monitored for 30 minutes after the furosemide administration (see Fig. 10-3), and urine output is monitored every 5 to 10 minutes to ensure that an adequate diuresis has been induced. If the diuresis response is inadequate, additional intravenous crystalloid solution and an additional dose of intravenous furosemide may be given at the discretion of the physician performing the pressure-flow study. A peak RPP after furosemide administration of 14 cm H_2O or lower is considered negative and nonobstructive, and a peak RPP greater than 14 cm H_2O is considered positive for significant obstruction.

In a series of more than 55 patients who received both individualized infusion and diuresis pressure-flow studies, the results from the two types of studies were congruent in all but 3 patients. In these 3 cases, the peak pressures straddled the 14 cm H_2O threshold for normal, and the test results were either borderline positive or borderline negative, but the peak RPPs obtained from the two forms of pressure-flow study were in fact different by only 2 to 3 cm H_2O. From these data, furosemide-induced diuresis presents a sufficiently rigorous flow challenge to the collecting system to yield RPP changes comparable to the alterations induced by an individualized external infusion.[29]

Because the results of the individualized infusion pressure-flow study and the diuresis pressure-flow study were similar, what then are the physiologic and practical differences between these two forms? The individualized infusion has the drawback that the infusion is somewhat nonphysiologic and does not account for changes in renal function, such as a decreased GFR, which may limit the kidney's ability to diurese, or renal tubular dysfunction, which may result in decreased concentrating ability and increased free water excretion. Furosemide-induced diuresis is more likely to reflect changes in renal functional status, because the flow challenge to the collecting system is generated from endogenous urine output, as opposed to an external electric pump. The strength of the individualized infusion pressure-flow study lies in the operator's having knowledge of the flow rates through the collecting system at all times during the study and being able to adjust the flow at will. The ability to challenge the collecting system with different infusion rates adds an extra dimension to the pressure-flow study; a sense of the severity of the obstruction is provided by examining what infusion rate the system can tolerate before the RPP becomes elevated. In addition, the use of supraphysiologic infusion rates provides a means of assessing the degree of reserve capacity in handling additional urine flow. The diuresis pressure-flow study, on the other hand, provides an answer that is simply positive or negative, with little information on the severity of obstruction or reserve capacity, because the exact urine flow rate cannot be ascertained.

Whereas these two forms of pressure-flow studies seem to be testing the collecting system similarly based on the basic principle (resistance $\propto$ pressure/flow), our current knowledge of the pathophysiology of renal obstruction suggests that there is a fundamental difference between these two tests. The individualized infusion pressure-flow study provides a measure of the resistance of the collecting system to flow. In contrast, we theorize that the diuresis pressure-flow study reveals the presence of a physiologically significant obstruction, which is defined as an impediment in urine transport that leads to compensatory changes in physiologic renal parameters, including but not limited to RPP, renal blood flow, and GFR.

As discussed earlier, the congenitally hydronephrotic kidney with ongoing obstruction always maintains a normal RPP and is indistinguishable from the nonobstructive kidney in baseline RPP. However, it most likely maintains by means of compensatory changes in renal blood flow and GFR, similar to what is well documented in acute obstruction models. RPP is normal in a nonhydronephrotic kidney because the normal collecting system has a huge reserve capacity for handling additional urine flow, whereas a congenitally hydronephrotic kidney with significant obstruction is able to maintain normal RPP because it has undergone compensatory reductions in renal blood flow and GFR to achieve a new equilibrium.

In this compensatory equilibrium, the obstructed kidney has little or no reserve for handling any increase in urine flow, and an elevation in RPP ensues when the system is challenged by an induced diuresis. In this setting, the furosemide-induced diuresis is more than just a flow challenge to the collecting system; it is in fact a means of “agitating” the significantly obstructed kidney into revealing the presence of a compensatory equilibrium. Therefore, a positive diuresis pressure-flow study (peak RPP >14 cm H_2O) is not merely evidence for a collecting system with abnormally high resistance to flow, but also, and more importantly, an indication that the kidney being tested is under a compensatory equilibrium state, precariously maintaining a normal RPP at the expense of decreased blood flow or GFR or both. By definition, a *physiologically significant obstruction* is present in such a kidney, and it is uncovered by the positive result of a diuresis pressure-flow study.

For these reasons, we believe that the diuresis pressure-flow study holds the promise of being the “gold standard” diagnostic tool in the assessment of hydronephrosis. Because this test is still relatively new, clinical data are still accumulating. In our current series of more than 55 patients, positive studies have correlated with a significantly higher proportion of patients who are symptomatic or show evidence of renal functional deterioration.[30] These correlations suggest that a positive diuresis pressure-flow study is predictive of *functionally significant obstruction*. Conversely, in our recent analysis of a group of patients with negative diuresis pressure-flow studies, none had shown evidence of deterioration or required surgical intervention for symptomatic complaints (Fig. 10-6).[31] At the limited follow-up of 2 years, the negative predictive value of diuresis pressure-flow study was 100%. Whereas these numbers are still small and follow-up is still limited, we are not aware of any other diagnostic modality that has been shown to have comparable correlation with clinical outcome. Pending further validation, we believe that the diuresis pressure-flow study will emerge as the next gold standard diagnostic tool in the assessment of hydronephrosis.

Although the diuresis pressure-flow study possesses many positive attributes as a diagnostic tool for the evaluation of hydronephrosis, it remains an invasive procedure. It is therefore important to clarify whether the diuresis pressure-flow study reveals uniquely important diagnostic information, compared with similar noninvasive procedures such as diuretic nuclear renography. The protocols for the diuresis pressure-flow study and diuretic nuclear renography share many important common features, including the use of a urethral catheter to keep the bladder empty, an intravenous crystalloid solution bolus to ensure adequate patient hydration, and the administration of 1 mg/kg of intravenous furosemide to challenge the collecting system with a diuresis. However, the key parameters assessed by the two studies are fundamentally different. Whereas the diuresis pressure-flow study examines RPP changes as urine flow increases, diuretic nuclear renography measures the washout half-life ($T_{½}$), a semiquantitative measure of the rate of flow of urine across the suspected site of obstruction. When we studied 46 hydronephrotic kidneys with both the diuresis pressure-flow study and diuretic nuclear renography, it was found that RPP alterations held no correlation with washout $T_{½}$, and these two variables were essentially independent of each other. When basic physical principles are taken into account, these results should come as no surprise: Because resistance is directly proportional to pressure divided by flow, resistance can be assessed only if both pressure and flow parameters are simultaneously taken into account. Although the diuresis pressure-flow study does take both pressure and flow into account, diuretic nuclear renography does not measure pressure; it only provides an indicator of urine flow by the measurement of washout $T_{½}$. The fact that RPP alterations hold no correlation with washout $T_{½}$ confirms that washout $T_{½}$ cannot be used as an indicator of the resistance of the collecting system. Some of the kidneys examined in our study showed evidence of significant obstruction with markedly increased collecting system resistance based on the diuresis pressure-flow study, yet the washout $T_{½}$ was normal. Conversely, some of the kidneys examined showed no evidence of significant obstruction with normal RPP throughout, yet the washout $T_{½}$ was grossly elevated. This potential for diuretic nuclear renography washout $T_{½}$ to be misleading was confirmed by a similar study in which the washout curve results were compared with infusion pressure-flow study results.[32] Therefore, washout $T_{½}$ should be regarded as an indicator of the rate of urine flow, as it was originally designed to measure. Washout $T_{½}$ does not take pressure into account and is therefore unlikely to be of substantial value in isolation in determining the resistance of the collecting system. To assess the resistance of the collecting system—specifically, the severity of the obstruction—percutaneous pressure-flow studies remain the most suitable diagnostic modality.

OTHER ATTRIBUTES OF THE URINARY TRACT RELEVANT TO UPPER TRACT URODYNAMICS

Urodynamic parameters of the upper urinary tract not only respond to obstruction and dilatation of the collecting system but also vary dynamically depending on their interaction with other parts of the urinary tract. To perform percutaneous pressure-flow studies in a physiologically meaningful manner and to interpret their results appropriately, it is important to take the influence of other relevant components of the urinary tract into account. Key attributes of the urinary tract that exert significant influences on upper tract urodynamics are discussed in the following sections.

Pressure Gradient between the Renal Pelvis and the Bladder

Pressure dynamics in the renal pelvis are not only influenced by the site of ureteral obstruction but also depend on contributions from the normal ureter distal to the suspected site of obstruction. A clear understanding of the effects of the normal distal ureter is crucial to a properly performed pressure-flow study. This section addresses how best to handle the pressure gradient that occurs between the renal pelvis and the bladder.

The contribution of active ureteral peristalsis to renal pelvis pressure dynamics is illustrated by a series of experiments we performed in a porcine model (Fung LCT et al, unpublished data, 2009). Because pressure-flow studies are performed only in hydronephrotic kidneys, there was a lack of normal controls for establishing what pressure-flow values might be encountered in nonhydronephrotic kidneys. In an attempt to obtain some guidelines as to how normal kidneys behave, we performed a series of pressure-flow studies in normal, nonhydronephrotic kidneys in pigs. An unanticipated scenario encountered during one of the infusion studies succinctly illustrates the active contribution by ureteral peristalsis to upper tract urodynamics. We were evaluating the capacity of a normal collecting system for handling additional flow and incrementally increasing the rate of infusion into the collecting system. In spite of increasing the infusion rate to more than five times the maximum physiologic urine output, the RPP was still maintained within a normal range. Unexpectedly, the RPP then suddenly became grossly elevated. To bring the

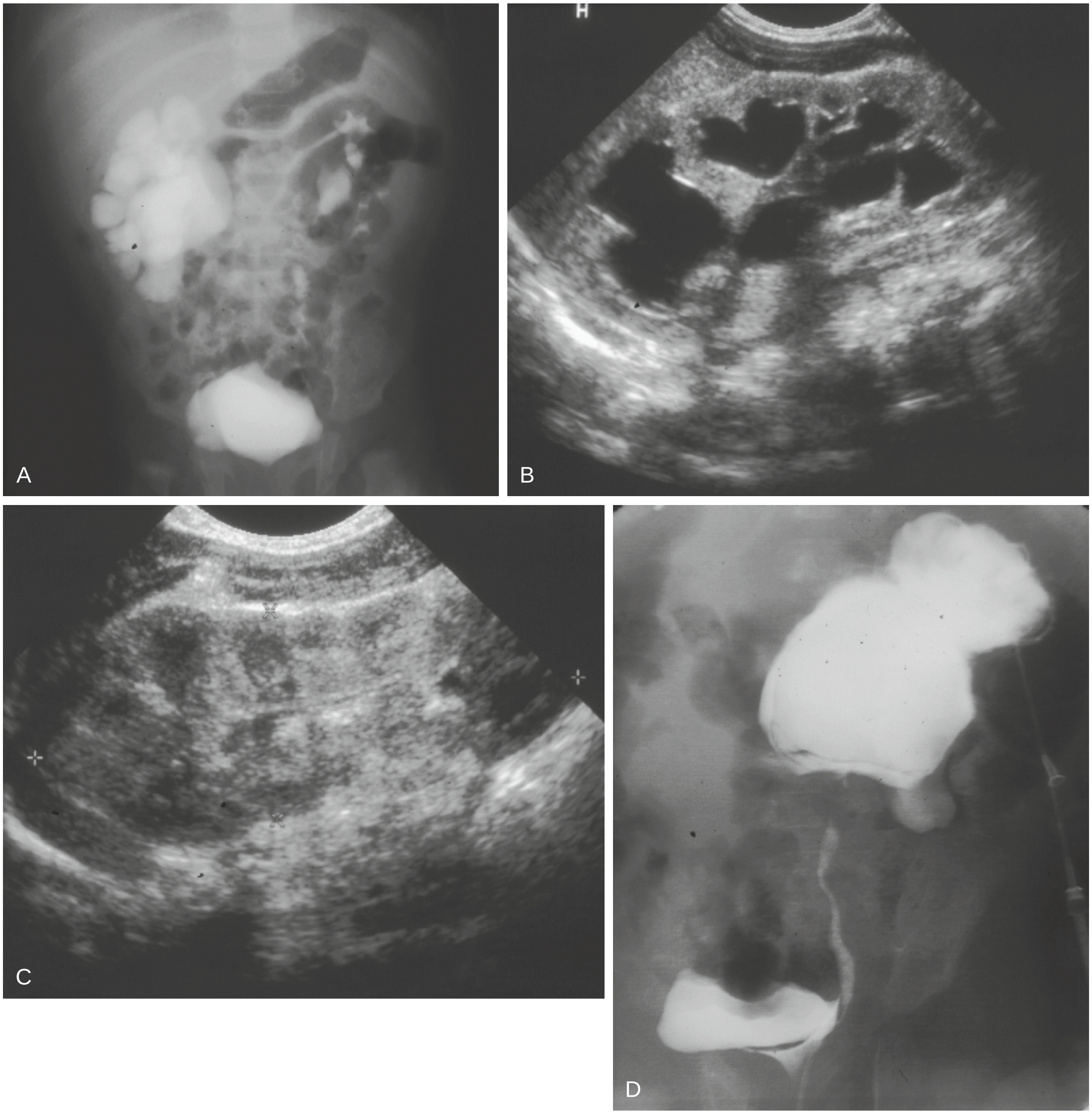

Figure 10-6 A male patient was identified as having right hydronephrosis compatible with ureteropelvic junction (UPJ) obstruction, as shown by an intravenous pyelogram **(A).** Ultrasonography demonstrates marked right hydronephrosis with significant thinning of the renal cortex **(B)** and a normal left kidney **(C).** A percutaneous pressure-flow study was performed when the patient was 7 weeks of age. **D,** A right antegrade nephrostogram with the patient in the prone position is shown. The pressure-flow study was negative for significant obstruction; the peak renal pelvic pressure was only 5 cm H_2O, well below the upper limit of normal (14 cm H_2O), under both furosemide-induced diuresis and a supraphysiologic infusion rate of 200%. Despite significant cortical thinning and pelvicaliectasis, the patient was managed with an observational approach in view of the negative pressure-flow study. His initial right differential renal function of 30% spontaneously improved to 52% after 1 year and further increased to 58% at his 2-year follow-up. It is unclear why the differential renal function increased to beyond 50%, but nevertheless the initial negative pressure-flow study was ineffective in excluding ongoing significant UPJ obstruction in this case.

RPP back to a normal range, the infusion rate had to be slowed to practically a complete stop. What could have accounted for such a dramatic and sudden change? We realized shortly afterward that the animal had expired partway through the study. It was the change from an active living ureter to a dead, nonperistalsing ureter that had caused the dramatic change in the ability of the system to handle high flow rates. The living ureter was so efficient that we had trouble increasing the already supraphysiologic infusion rate to a rate sufficiently high to cause an elevation in RPP, whereas the dead, nonperistalsing ureter could not handle even modest physiologic infusion rates. This observation clearly illustrates that a living ureter with active peristalsis is not just a hollow conduit but a highly effective, active urine transport mechanism.

In the seven animals that we studied, it was consistently observed that the normal collecting system had a tremendous capacity for handling extremely high flow rates. Extrapolating these findings in normal pig kidneys to human pressure-flow studies, a hydronephrotic kidney that exhibits RPPs of less than 14 cm H_2O under optimal flow challenge would be considered satisfactory in drainage efficiency. However, its reserve capacity for handling additional urine flow may be significantly diminished compared with that of a normal collecting system. To assess for this reserve capacity, we now routinely employ supraphysiologic infusion rates, provided that the pressure-flow study was initially negative. If the RPP remains well below 14 cm H_2O during the diuresis component and at the individualized infusion rate, the infusion rate is increased further by 50% or 100% above the calculated maximum physiologic urine output. As previously discussed, the supraphysiologic infusion rate provides a measure of the reserve capability of the collecting system in handling extra fluid load; however, an elevated RPP (>14 cm H_2O) in this setting is not necessarily indicative of significant obstruction that requires surgical intervention, because the supraphysiologic infusion rate represents a flow rate that exceeds normal physiologic urine output.

By obtaining a sense of the reserve capacity for handling additional flow, collecting systems that are truly efficient in urine transport can be distinguished from ones that are barely able to cope. Whereas a collecting system with little or no reserve capacity may not require surgical intervention at that particular time, such a kidney is, in fact, already significantly compromised compared with the truly physiologically normal collecting systems observed in the pig experiments. Therefore, a hydronephrotic kidney that is found to have little or no reserve capacity for supraphysiologic flow rates may not require surgical intervention at the time the pressure-flow study was performed but should be closely monitored with a high index of suspicion for future deterioration.

Given that the ureter acts as an active peristaltic pump, as opposed to a passive fluid conduit, the pressure gradient between the renal pelvis and the bladder may not remain constant, as was presumed by Whitaker.[22] Whitaker proposed that the RPP and intravesical pressure should both be monitored during a pressure-flow study. The test result should then be interpreted according to the subtracted RPP (that is, the RPP minus the intravesical pressure, referred to by Whitaker as the *relative pressure*), a calculation that would effectively eliminate the pressure gradient between the renal pelvis and the bladder. To evaluate whether this relationship holds true, we assessed 19 hydronephrotic kidneys using the diuresis pressure-flow study, in which the intravesical pressure was systematically varied. Once optimal diuresis was induced and peak RPP was reached, the bladder, which had been kept empty by an indwelling catheter, was filled to an intravesical pressure of first 10 and then 20 cm H_2O. As the intravesical pressure increased from 0 to 10 cm H_2O and then to 20 cm H_2O, it was observed that the RPP did not increase linearly in every case. Some of the kidneys exhibited RPPs that remained constant despite alterations in intravesical pressure, but other kidneys exhibited RPPs that increased rapidly and disproportionately to the increase in intravesical pressure (Fig. 10-7).

These studies serve to illustrate that the ureter actively regulates upper tract urine transport and does not maintain a constant gradient between the renal pelvis and the bladder. The concept of a constant, unchanging pressure gradient between the renal pelvis and the bladder, as assumed by Whitaker, has been shown not to be valid, and the calculated "subtracted RPP" would logically contain significant built-in biases. Therefore, we advocate the alternative approach of performing pressure-flow studies with the bladder kept empty via an indwelling catheter. Instead of trying to account for the influence of intravesical pressure on the upper tract, the intravesical pressure is simply kept at 0 cm H_2O by maintaining an empty bladder. Intravesical pressure monitoring is no longer necessary, so long as an empty bladder can be periodically verified during the pressure-flow study by fluoroscopic monitoring.

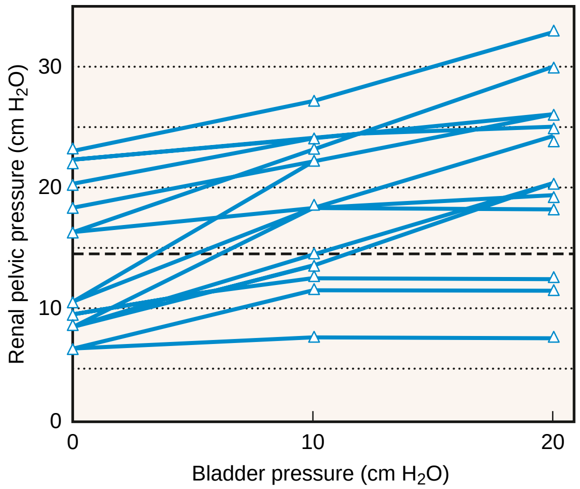

Figure 10-7 Diuresis pressure-flow studies were performed in 19 hydronephrotic kidneys, with the bladders initially kept empty by an indwelling catheter. Once optimal diuresis was induced and peak renal pelvic pressure (RPP) was reached, the intravesical pressure was then systematically varied by filling the bladder. As the intravesical pressure increased from 0 to 10 cm H_2O and then to 20 cm H_2O, it was observed that the RPP did not always increase linearly. Whereas some of the kidneys exhibited RPPs that remained constant despite alterations in intravesical pressure, others exhibited RPPs that increased rapidly and disproportionately to the increase in intravesical pressure.

The Effects of Vesicoureteral Reflux on Upper Tract Urodynamics

The fact that the RPP does not necessarily increase in a linear fashion as intravesical pressure varies, as described in the previous section, is undoubtedly in part a result of the peristaltic action of the ureter, which enables active transport of urine into the bladder despite a positive pressure gradient. However, the ability for the RPP to remain independent of intravesical pressure also relies on a nonrefluxing UVJ. In the presence of VUR, the incompetent UVJ is more prone to transmit intravesical pressure proximally back to the ureter (Fig. 10-8). Therefore, upper tract urodynamics can be expected to be significantly influenced by intravesical pressure whenever VUR is present.

The way in which intravesical pressure affects upper tract pressure depends on the intravesical pressure at which VUR begins to occur and whether the intravesical pressure is greater or less than the RPP. In addition to the patients in which we performed a diuresis pressure-flow study with systematic variation of the intravesical pressure (see previous discussion), three patients with VUR were also studied (Lakshmanan Y et al, unpublished data, 2009). Although the observations made in only three patients were insufficient for establishing any statistically valid conclusions, they were consistent with the following, intuitively logical pattern. In the presence of VUR, the RPP (i.e., the upper tract pressure proximal to the site of obstruction) is theoretically independent of the intravesical pressure only so long as the intravesical

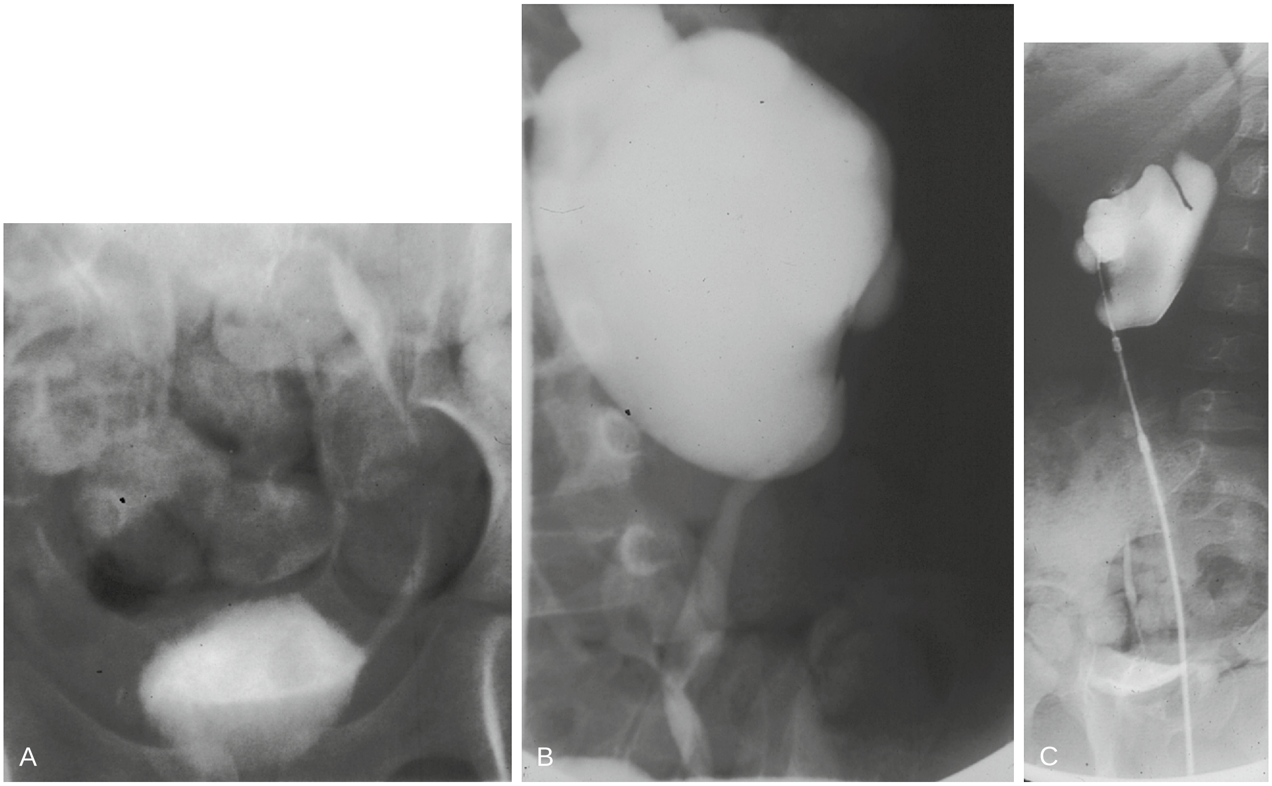

Figure 10-8 Voiding cystourethrogram in a 3½-year-old girl shows vesicoureteral reflux (VUR) into a nondilated left ureter compatible with grade II reflux **(A),** and yet the renal pelvis and calyces are disproportionately severely dilated **(B).** This discrepancy in pelvicaliectasis that exceeds the degree of dilatation usually associated with low-grade reflux suggests the concomitant presence of ureteropelvic junction (UPJ) obstruction. A percutaneous diuresis pressure-flow study confirmed high-grade left UPJ obstruction. After the administration of intravenous furosemide, the left renal pelvic pressure rose to 63 cm H_2O, the highest value we have recorded to date. There was no efflux of contrast material across the left UPJ, compatible with a Dietl crisis-type intermittent high-grade UPJ obstruction induced by diuresis. A left antegrade nephrostogram with the patient in the prone position is shown **C.**

pressure remains at 0 cm H_2O. If the intravesical pressure rises above 0 cm H_2O but is still lower than the pressure at which VUR begins to occur, the RPP may increase to some degree, but not necessarily in a linear relationship to the increase in intravesical pressure (much like the nonrefluxing renal units described earlier). If the intravesical pressure rises beyond the point at which VUR begins to occur, it begins to have a much more direct effect on RPP. If the intravesical pressure then becomes greater than the RPP, the RPP in time equilibrates with the intravesical pressure and the two become equal.

These observations in patients with VUR underscore the erratic nature of the interaction between intravesical pressure and upper tract pressure. Whereas the pressure gradient between RPP and intravesical pressure was already found to be nonlinear in nonrefluxing renal units, their interaction is especially complex in the presence of VUR. If filling of the bladder were to be allowed during a pressure-flow study, as was originally described as part of a Whitaker test, this complex and nonlinear interaction would preclude any meaningful analysis of upper tract urodynamic parameters even if the intravesical pressure were continuously monitored. These considerations provide further support for the approach described previously of using catheter drainage to maintain an empty bladder (effectively 0 cm H_2O) throughout the pressure-flow study. A well-emptied bladder is especially important to pressure-flow studies performed in patients with VUR and coexisting upper tract obstruction and should be diligently verified by periodic fluoroscopy.

Pressure Decay, Capacity, and Compliance of the Collecting System

The higher the capacity and compliance are in a collecting system, the greater is the increase in volume required before a change in RPP occurs.[33,34] This relationship pertains to the assessment of hydronephrotic kidneys with relatively small pelvicalyceal systems, rather than kidneys with a hugely dilated renal pelvis or hydroureteronephrosis with both a dilated renal pelvis and a capacious ureter. In practical terms, the capacity and compliance affect how a pressure-flow study is performed only in terms of the importance of achieving maximal filling of the collecting system during the study. In a hugely capacious collecting system, RPP may remain within normal limits at first, despite optimal flow challenge; it is not until the system reaches its capacity that the true peak RPP can be meaningfully evaluated. Therefore, whether the pressure-flow study is performed by diuresis or by infusion, it is crucial to monitor the distention of the collecting system fluoroscopically. Peak RPP should be determined only after optimal flow challenge has been established and the collecting system can be fluoroscopically verified to have been filled to a satisfactory degree. Consistent with these considerations, we have found that patients with UVJ obstruction and hugely dilated ureters require a longer time before peak RPPs are reached, compared to those with UPJ obstruction and relatively small pelvicalyceal systems.

As a means of understanding how a collecting system handles high-pressure states, we studied the concept of pressure decay in hydronephrotic kidneys.[35] *Pressure decay* is defined as the natural decline in collecting system pressure that occurs once the flow challenge to the collecting system has ceased. Because a furosemide-induced diuresis cannot be turned on and off at will, pressure decay is best analyzed using the infusion pressure-flow study. We studied 43 hydronephrotic kidneys and incrementally increased the infusion rate until an RPP of 40 cm H_2O was reached. The infusion was then abruptly discontinued, and the subsequent decline in RPP was continuously monitored. The natural decline in RPP (i.e., the pressure decay) was then plotted over time as a *pressure decay curve* (Fig. 10-9). The pressure decay curve can be mathematically analyzed to calculate its decay half-life (*pressure decay* $T_{½}$), which reflects the time required for the collecting system to decline to one half of its initial RPP.

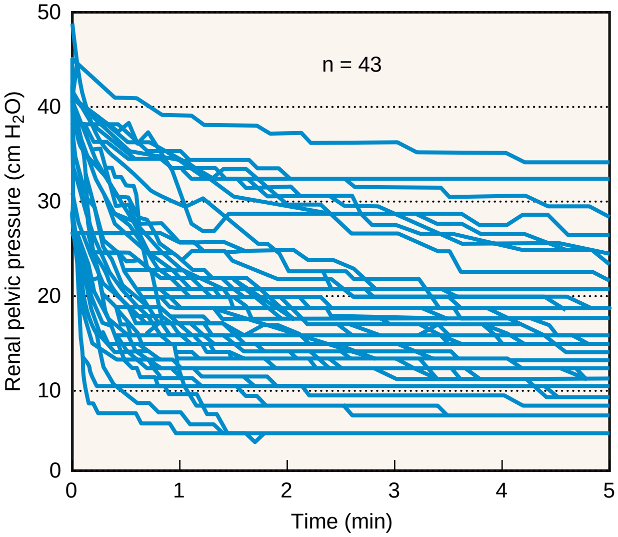

Figure 10-9 Pressure decay curves show the decline in renal pelvic pressure over time after cessation of nephrostomy infusion in 43 patients.

In order to calculate pressure decay $T_{½}$, the pressure decay curves were first mathematically translated so that the convergence point equaled zero and then semilogarithmically transformed. First-order (straight-line) curves achieved excellent fits, as evidenced by a mean curve fit coefficient of 0.92 (range, 0.83 to 0.99). The pressure decay $T_{½}$ values calculated from these semilogarithmic curves were numerically consistent with the visual observations made on inspection of the pressure decay curves. The group with efficient urine transport according to the individualized pressure-flow study had a mean pressure decay $T_{½}$ of 0.36 ± 0.22 minutes, whereas the group with inefficient urine transport had a mean pressure decay $T_{½}$ of 3.47 ± 2.77 minutes (Fig. 10-10). The two groups had significantly different pressure decay $T_{½}$ values ($P < .0001$). These data suggest not only that inefficient collecting systems are prone to developing elevated RPPs but also that the elevated RPP tends to persist longer as a result of the inefficient urine transport. Conversely, not only do efficient collecting systems protect the renal unit from developing elevated pressure, but also, even if high pressures are transiently present, they are generally able to return the elevated pressure to normal rapidly, by means of the efficient urine transport.

Even though the correlation between urine transport efficiency and pressure decay $T_{½}$ was very strong, there was some overlap in the results between the efficient and the inefficient groups. In other words, some efficient collecting systems had relatively high pressure decay $T_{½}$ values, and some inefficient collecting systems had relatively short pressure decay $T_{½}$ values, contrary to the general overall pattern. This overlap may be attributable to differences in compliance and in the volume of the collecting system proximal to the level of outflow restriction. A relatively noncompliant collecting system responds to small volume increments with large pressure changes, whereas a highly compliant collecting system requires relatively large volume changes to produce a relatively small pressure change.[36] Applying this principle to the pressure decay curves, one would expect that, even if two collecting systems have identical overall outflow resistance, the system with the lower compliance should have a more rapid pressure decay because it has to drain only a relatively small volume to bring its pressure down, compared with the

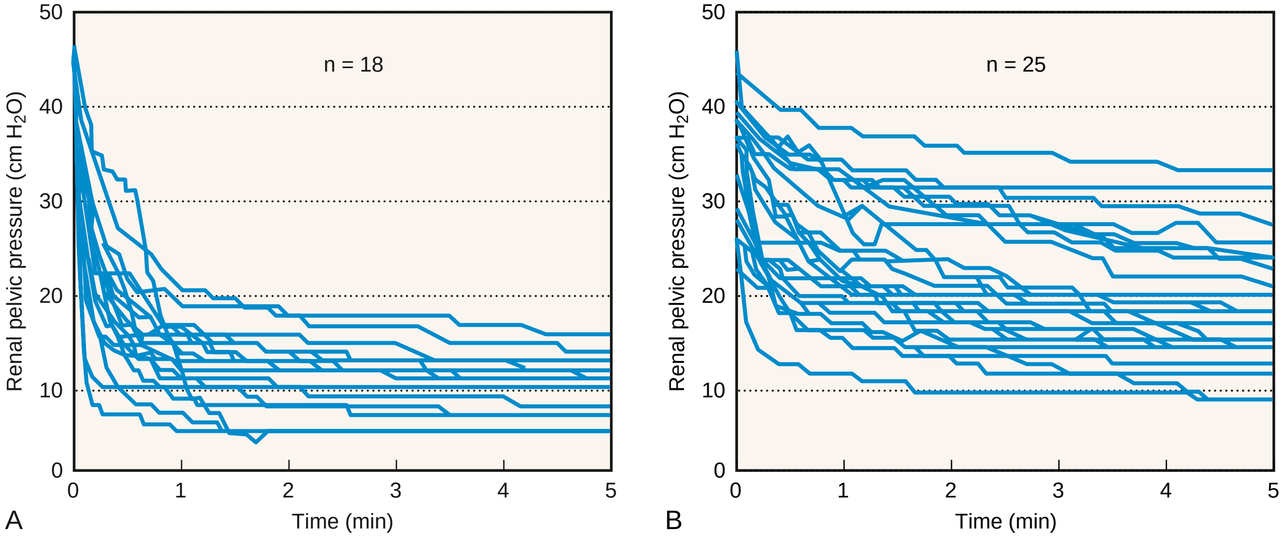

Figure 10-10 Pressure decay curves (renal pelvic pressure [RPP] versus time) are separated into two groups based on the individualized pressure-flow study results. The group with efficient urine transport according to the individualized pressure-flow study (peak RPP ≤14 cm H_2O) had a mean pressure decay $T_{½}$ of 0.36 ± 0.22 minutes **(A),** whereas the group with inefficient urine transport (peak RPP >14 cm H_2O) had a mean pressure decay $T_{½}$ of 3.47 ± 2.77 minutes **(B).**

more compliant system. Similarly, the volume of the proximal collecting system also plays an important role in the pressure decay dynamics. Consider the situation in which two collecting systems have the same outflow resistance but one has a larger renal pelvis than the other: even though their pressure decay curves would begin with drainage at identical rates, the larger collecting system would drain a smaller percentage of its total volume during any given period and would have a slower pressure decay as a result.

These theoretical considerations demonstrate that the pressure decay $T_{1/2}$ is not a specific measurement of outflow resistance but is in part determined by the compliance and volume of the collecting system. It is therefore not surprising that some efficient collecting systems had relatively high pressure decay $T_{1/2}$ values whereas some inefficient systems had relatively short pressure decay $T_{1/2}$ values. Consequently, in spite of the overall strong correlation between urine transport efficiency and the pressure decay $T_{1/2}$, the pressure decay $T_{1/2}$ should not be used in isolation as the sole diagnostic criterion for physiologically significant hydronephrosis. If used in conjunction with other diagnostic modalities, however, the pressure decay $T_{1/2}$ provides an objective, quantitative measure of the relative tendency for elevated RPPs to persist.[35]

In addition to the differences in renal pelvic compliance, the anatomic configuration of the UPJ also plays a role in pressure decay. In three of the pressure decay curves, the pattern of RPP decline showed two distinctly different phases. The decline in RPP was initially very slow, with the RPP remaining relatively high for several minutes after the infusion was stopped. Once the RPP was less than approximately 25 cm H_2O, however, the remainder of the pressure decay curve declined to normal exceedingly rapidly. Fluoroscopically, these renal units were demonstrated to have UPJs that changed in configuration as the renal pelvis filled, and all of these patients had a history of intermittent flank pain (Fig. 10-11). The usefulness of fluoroscopic monitoring on kidneys with intermittent obstruction is further discussed in the next section.

Whereas the concept of pressure decay provides important insight into how a collecting system handles elevated pressure once the flow challenge abates, the pressure decay $T_{1/2}$ is not specific for diagnosing obstruction and is significantly influenced by the capacity and compliance of the collecting system. Therefore, we currently do not use the pressure decay concept as a routine part of our pressure-flow study protocol.

Fluoroscopic Monitoring, Ureteral Opening Pressure, and Intermittent Obstruction

At the beginning of a pressure-flow study, contrast material may be instilled into the renal pelvis to verify proper positioning of the nephrostomy access. An equivalent volume of urine should first be aspirated before the instillation of contrast material, so that the baseline pressure dynamics of the renal pelvis remain unchanged. With contrast material present in the renal pelvis, subsequent RPP changes can be correlated with dynamic anatomic alterations by periodic fluoroscopic monitoring over the course of the pressure-flow study. In this regard, the individualized infusion pressure-flow study provides superior imaging details compared with the diuresis pressure-flow study, because contrast material is continuously infused into the collecting system and is not subjected to the effects of a diuresis diluting the contrast material. Three

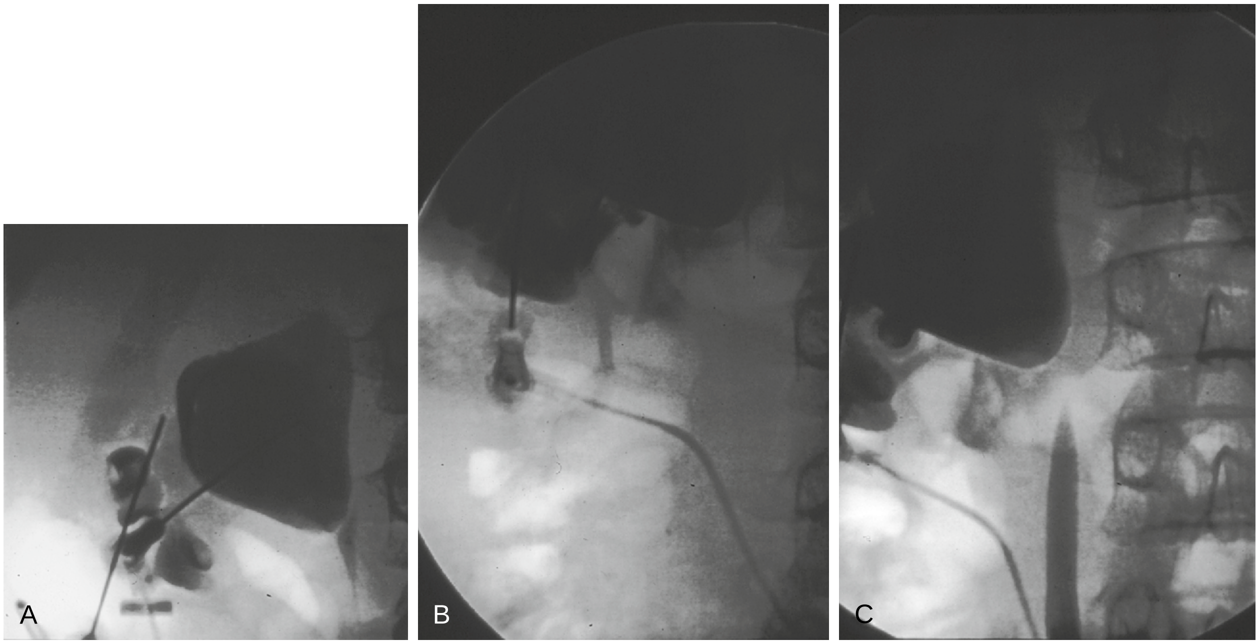

Figure 10-11 This 6-year-old girl was initially misdiagnosed as having a chronic gastrointestinal disorder when she presented with recurrent abdominal pain, nausea, and vomiting. **A,** When she underwent a percutaneous pressure-flow study to evaluate her left hydronephrosis, contrast material was seen to drain across the ureteropelvic junction (UPJ) into the proximal ureter early in the study. **B,** As the renal pelvis became progressively more distended, the drainage of contrast material across the UPJ ceased entirely. Renal pelvic pressure continued to rise sharply, and the pressure-flow study was terminated at 40 cm H_2O. No drainage of contrast material was seen across the UPJ until fluid was aspirated out of the renal pelvis to decompress the grossly distended collecting system. **C,** When the renal pelvis dimension returned toward its initial baseline, drainage across the UPJ resumed with a gush of contrast material into the proximal ureter. This pattern of intermittent high-grade obstruction was presumed to be secondary to a kink at the UPJ that was accentuated by overdistention of the renal pelvis. Her recurrent abdominal pain, nausea, and vomiting episodes (Dietl crises) were successfully corrected by a dismembered pyeloplasty.

helpful uses have been observed from the fluoroscopic monitoring of the collecting system during pressure-flow studies.

First, the antegrade nephrostograms obtained from capturing relevant images provide anatomic details of the obstructive site or sites that are helpful for planning the most appropriate surgical repair (Fig. 10-12). In some high-grade obstructions, however, there may be little or no contrast material flowing past the site of obstruction, and the ureter distal to the site of obstruction cannot be visualized. Retrograde pyelography would handily provide this missing information if necessary.

As a second utility of fluoroscopic monitoring, the RPP at which antegrade contrast material is first seen distal to the suspected site of obstruction can be observed. This is defined as the *ureteral opening pressure* (Fig. 10-13).[37] In a study of 52 renal units in 43 patients, positive ureteral opening pressures (>14 cm H_2O) had a 100% association with a positive individualized infusion pressure-flow study. When the ureteral opening pressure was negative (≤14 cm H_2O), however, it was predictive of a negative individualized infusion pressure-flow study in only 57% of the cases. There were no false-positive ureteral opening pressures, using the individualized infusion pressure-flow study as the reference point. In other words, a positive ureteral opening pressure can be taken as strong corroborative evidence that abnormally high resistance is present in the collecting system in question, but a negative ureteral opening pressure does not rule out significant obstruction.

Third, fluoroscopic monitoring is particularly helpful in assessing patients who present with intermittent pain, in whom the origin of pain can at times be difficult to ascertain and easily confused with gastrointestinal or even psychogenic disorders. On pressure-flow studies, these patients have a typical pattern in which they start off with what appears to be relatively efficient collecting system drainage. As the flow rate increases, whether it is induced by furosemide or challenged by an external infusion, the renal pelvis becomes increasingly dilated, and the UPJ can be seen to be progressively displaced. This displacement of the UPJ eventually results in kinking of the UPJ, leading to an acute high-grade obstruction in which little or no flow can move through the UPJ (see Fig. 10-11). As the obstruction worsens acutely, the RPP typically also becomes markedly elevated. As the infusion stops or the diuresis abates, the process essentially reverses itself. The initial decline in RPP is very slow, with minimal flow passing through the UPJ, but after it reaches the threshold at which the UPJ kinking initially occurred, the UPJ can be seen to suddenly open up. At this point, the renal pelvis empties rapidly and the RPP soon returns to normal. When this typical pattern is demonstrated by the simultaneous use of pressure-flow parameters and fluoroscopic images, the intermittent nature of such high-grade UPJ obstruction can be diagnosed with certainty.

Multiple Sites of Ureteral Obstruction

In the evaluation of hydronephrosis, it is not uncommon to encounter more than one possible site of ureteral obstruction. Any two or more conditions that lead to ureteral obstruction can combine to produce an additive obstructive effect on the kidney. The most commonly seen combinations of multiple sites of ureteral obstruction arise from having ureteral hypoperistaltic segments present at two or more levels, including simultaneous UPJ and UVJ obstruction; UPJ, midureteral, and

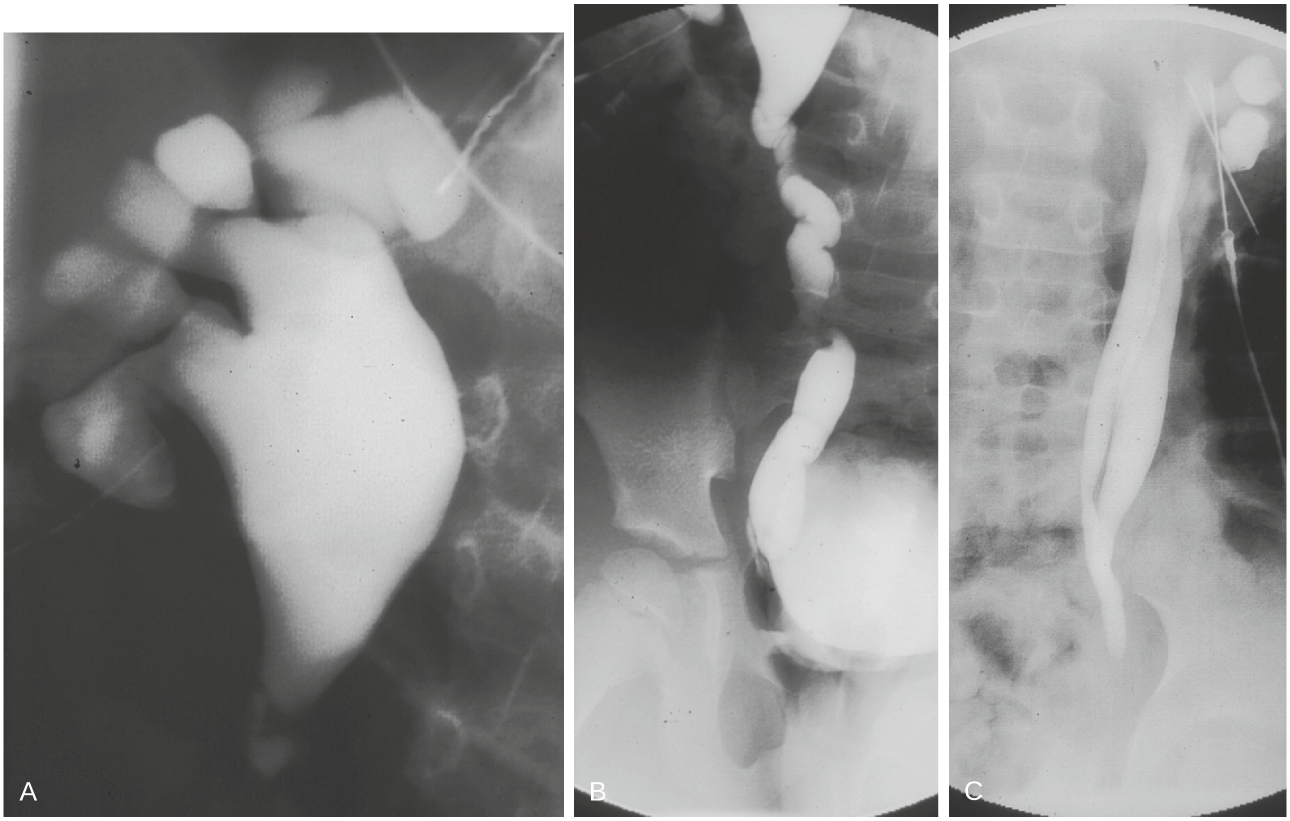

Figure 10-12 **A** and **B,** Antegrade nephrostograms can provide excellent anatomic detail, such as in this 5-year-old boy in whom there are multiple anomalies at the ureteropelvic junction, midureter, and ureterovesical junction levels. **C,** In a 4-year-old girl, partial ureteral duplication is identified.

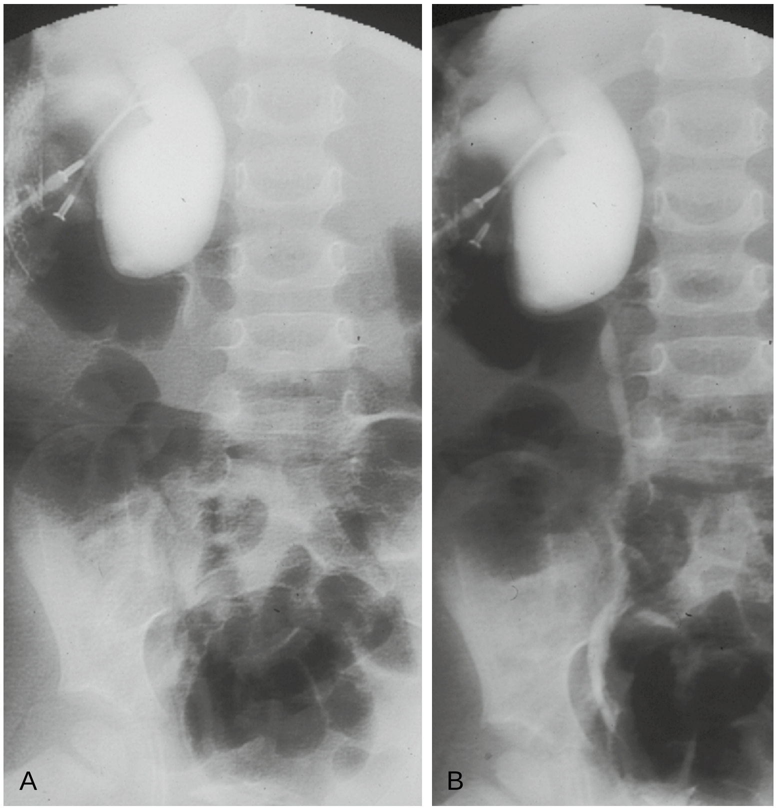

Figure 10-13 Ureteral opening pressure is defined as the pressure at which antegrade contrast is first seen distal to the suspected site of obstruction. In this 4-year-old boy with left hydronephrosis, no contrast was seen to enter the ureter (**A,** left antegrade nephrostogram in prone position) until his left renal pelvic pressure reached 17 cm H_2O **(B).** This ureteral opening pressure is compatible with significant ureteropelvic junction obstruction.

UVJ obstruction (see Fig. 10-12); and sequential hypoperistaltic segments involving the UPJ and the proximal ureter like a string of beads (Fig. 10-14).

Based on the principle that elevation in RPP constitutes the initial physical stimulus triggering the obstruction-induced compensatory cascade (see Pathophysiology), it would be logical to conclude that only the pressure effects directly perceived by the renal parenchyma have an impact on subsequent alterations in renal physiology. Thus, the collecting system pressure immediately adjacent to the renal parenchyma would ultimately determine the effects of obstruction on the kidney, regardless of whether one level or multiple levels of ureteral obstruction are present. In other words, RPP as recorded in a typical percutaneous pressure-flow study should be equally applicable to situations in which there are multiple sites of obstruction in the collecting system, provided there is no significant obstruction proximal to where the RPP is recorded, such as infundibular or calyceal stenosis.

Whereas a percutaneous pressure-flow study should be equally applicable to single-level and multiple-level ureteral obstructions, the result of the study is primarily helpful only in determining whether there is physiologically significant obstruction present as a result of the combined effect of all levels of ureteral obstruction. The alterations observed in RPP do not allow us to selectively discern the contribution from each individual level of obstruction to the overall obstructive effect. Nevertheless, observations of the antegrade transit of contrast material and ureteral peristalsis by real-time fluoroscopy can provide important clues to guide the clinician in formulating an appropriate treatment plan. For example, if contrast material can be seen passing through a proximal site of obstruction at low RPP but it is held up at a more distal obstructive site with subsequent progressive elevation in RPP, the more distal site constitutes the more significant site of obstruction. Conversely, if a proximal level of obstruction is seen to produce a holdup of contrast material along with an elevation in RPP, and any contrast material that transits across is promptly cleared by the more distal sites of obstruction, then the most proximal site constitutes the most significant level of obstruction. In this situation, however, repair of the proximal site may increase the rate of urine flow to the more distal obstructive sites. A previous seemingly innocuous ureteral narrowing

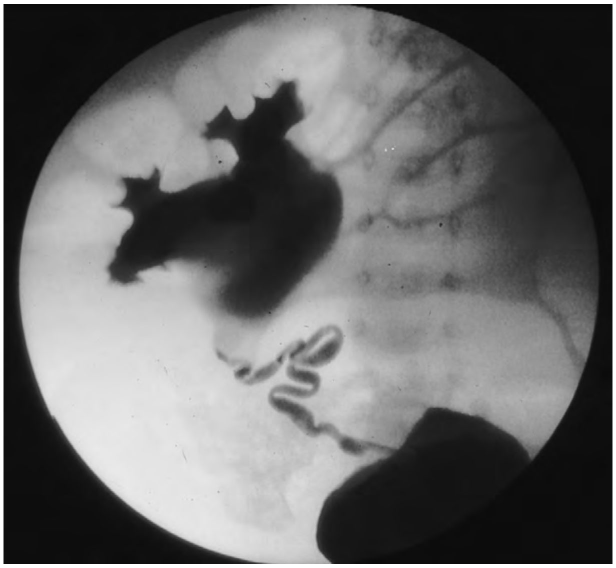

Figure 10-14 Retrograde pyelogram in a 3-month-old patient demonstrates right hydronephrosis and a right ureter with apparent anomalies at multiple levels of the ureter.

distal to the repaired site of obstruction could then become a significant site of ureteral obstruction challenged by the normalized proximal urine flow.

Formulation of a treatment plan in a case in which there is more than one level of anatomic anomaly can be quite a challenge to the clinician. The percutaneous pressure-flow study can still be used to determine whether there is physiologically significant obstruction, but the result of the study reflects the overall effect of all levels of anomalies combined and does not specifically assess the respective contribution from each individual level of anomaly. If significant obstruction is confirmed, it remains subjective for the clinician to determine whether only one, some, or all of the anatomic anomalies require surgical correction. If a single standard surgical incision can provide adequate exposure to all levels of anomaly, and if all anomalies can be safely and effectively corrected simultaneously, it is prudent to have all potentially significant obstructive sites corrected. However, in situations in which the correction of all suspected sites of obstruction would require multiple incisions or even multiple staged surgeries, the likelihood that a given level of anomaly is significantly obstructive would have to be weighed against the extent of surgery necessary to achieve an effective repair.

Among the currently available diagnostic modalities, the real-time fluoroscopic images of antegrade transit of contrast material coupled with RPP readings obtained during a percutaneous pressure-flow study provide some of the most comprehensive and dynamic diagnostic information. Nevertheless, the ultimate treatment plan remains subjective. As a result of these uncertainties, close longitudinal follow-up assessments remain the most important proof of the success of treatment, regardless of the chosen course of management.

Effects of Lower Tract Anomalies

Any lower urinary tract anomalies that result in an excessively high intravesical pressure can secondarily influence upper tract urodynamics, especially if VUR is present. Excessively high intravesical pressure can result from bladders that have decreased compliance or capacity and from those that empty poorly. Examples of such lower tract anomalies include neuropathic bladder dysfunction and urethral outflow obstruction (e.g., posterior urethral valves). In the assessment of these conditions, it is not unusual to encounter both upper tract hydronephrosis and lower tract urodynamic abnormalities simultaneously. If it is not immediately apparent from conventional imaging studies whether the upper tract hydronephrosis is a primary congenital abnormality separate from the lower tract anomaly or whether the hydronephrosis is secondary in nature and occurs as a result of the lower tract changes, the percutaneous pressure-flow study can be invaluable in making this important clinical distinction.

When percutaneous pressure-flow studies are performed in patients with concomitant lower urinary tract anomalies, effective catheter drainage of the bladder during the study is critical. The empty bladder renders the intravesical pressure 0 cm H_2O by definition and negates any potential influences of the lower tract anomaly on the upper tract urodynamics. The result of the pressure-flow study would thus reflect only the status of upper tract urine transport, in complete isolation from the effects of the lower urinary tract.

By assessing the upper and lower tract abnormalities separately (percutaneous pressure-flow study for the upper tract and video-urodynamic study for the lower tract), interpretation of results becomes greatly simplified. If clear-cut results are obtained from these studies, more detailed analysis of the interaction between the upper and the lower tract is probably unnecessary. For example, if a percutaneous pressure-flow study is performed with the bladder emptied by catheter drainage and the test result is unequivocally positive for upper tract obstruction, the collecting system has primary anomalies obstructive to the upper tract in addition to the lower tract anomalies. Conversely, if the pressure-flow study is unequivocally normal, there is no intrinsic obstruction to the upper tract collecting system, and whatever degree of hydroureteronephrosis is present has occurred secondarily as a result of the lower tract anomalies. If the initial pressure-flow study results are equivocal, however, what appears to be an insignificant degree of abnormality for both the upper and the lower tract may be combining to produce physiologically significant obstruction.

In situations in which the separately performed upper and lower tract urodynamic studies produce equivocal results, the percutaneous pressure-flow study can theoretically be performed in such a way as to reflect the combined physiologic effects of both the upper and the lower tract anomalies (see Fig. 10-10). To accurately reproduce the maximum effect that the lower tract abnormality may have on the upper tract urodynamics, the upper tract may be challenged with the peak intravesical pressure that occurs on a day-to-day basis in the particular patient being tested. This peak intravesical pressure would be most accurately ascertained by performing an ambulatory natural fill cystometric study. However, such information is often not available. As a substitute, we propose using the intravesical pressure measured at the beginning of a urodynamic study, when the patient begins the lower tract urodynamic study with what is considered a full but not unusually overdistended bladder. In this way, the intravesical pressure of a full bladder should approximate the peak intravesical pressure encountered on an average day. In contrast, the peak intravesical pressure encountered during an infusion cystometrogram should not be used as a challenge during percutaneous pressure-flow studies. In an infusion cystometrogram, the degree of bladder filling is somewhat arbitrary, and the irritative effects of the high infusion rate are known to produce supraphysiologic intravesical pressures. These confounding variables tend to contribute to an overestimation of the naturally occurring peak intravesical pressure.

Once the naturally occurring peak intravesical pressure is established, this value can be used to simulate the maximal effect that the lower tract anomaly may have on upper tract urine transport. We begin the percutaneous pressure-flow study with the usual arrangement of having the bladder kept empty by means of an indwelling catheter. Once the appropriate peak intravesical pressure is established, regardless of whether a diuresis pressure-flow study or an individualized infusion pressure-flow study is used, an additional challenge is presented to the upper tract by raising the intravesical pressure to the previously determined naturally occurring peak. This elevation in intravesical pressure can be achieved simply by connecting a saline solution drip to the indwelling bladder catheter. The drip chamber can then be raised to a level the same number of centimeters above the bladder as the naturally occurring peak intravesical pressure expressed in centimeters of water. When the saline solution drip slows to only intermittent drips or stops, one can determine that the desired elevation in intravesical pressure has been achieved. The resulting RPP recorded in this setting represents the combined effects of both the upper and the lower tract anomalies on upper tract urine transport, under conditions that challenge the collecting system maximally.

We do not have a sufficiently large experience in these highly selective cases to draw definitive conclusions regarding the diagnostic utility of this approach. However, our experience has confirmed that the additional challenge to the upper tract urine transport achieved by raising the intravesical pressure can indeed convert an equivocal result (peak RPP increased from baseline but remaining ≤14 cm H_2O) to a result that is clearly positive for physiologically significant obstruction (peak RPP well above 14 cm H_2O). These data serve as further proof of the close interaction between upper and lower tract urodynamics and underscore the importance of taking the combined effects of both upper and lower tract anomalies into account simultaneously, so that the most appropriate course of clinical management can be determined.

CURRENT CLINICAL ROLE FOR PERCUTANEOUS PRESSURE-FLOW STUDIES

A properly performed percutaneous pressure-flow study is a powerful diagnostic tool in the evaluation of hydronephrosis. It provides important diagnostic information distinguishing collecting systems that have a physiologically significant increase in resistance to urine flow from those systems that have innocuous dilatation but otherwise normal urine transport efficiency. However, it is a relatively complex and invasive diagnostic procedure, and it is not suitable for the evaluation of all hydronephrotic kidneys. In order to utilize noninvasive alternative diagnostic tools whenever possible but also to detect significant obstruction requiring surgical correction in a timely fashion, percutaneous pressure-flow studies should be performed only in appropriately selected cases.

Imaging studies that provide only anatomic details, such as ultrasonography, are noninvasive and simple to perform but are unable to quantitate renal function or physiologic alterations secondary to significant obstruction. Therefore, ultrasonography is primarily useful as a screening tool for hydronephrosis and for the follow-up evaluation of kidneys that are judged not to be in immediate need of surgical relief of obstruction. Hydronephrotic kidneys that are suitable for serial follow-up evaluation with ultrasonography alone include kidneys with a dilated renal pelvis and/or ureter but no caliectasis (grades I and II hydronephrosis by Society of Fetal Urology classification) and kidneys that have undergone successful surgical relief of obstruction but require further follow-up for stable or gradually improving residual collecting system dilatation. Kidneys that are at higher risk for deterioration and kidneys that demonstrate progressive dilatation on serial ultrasonography require further assessment by other diagnostic studies to evaluate functional or physiologically relevant parameters.

Nuclear medicine renal scans constitute the key diagnostic tools in the evaluation of renal function. Whereas the quantitation of differential renal function is only a relative measurement comparing one kidney with the contralateral mate, differential renal function remains the mainstay for judging whether renal function is stable or deteriorating over time. One strategy for determining when surgical correction is necessary for the relief of obstruction relies on alterations in differential renal function. Any decline in differential renal function greater than a predetermined level is used as an indicator of functionally significant obstruction, for which surgical relief of obstruction is then instituted. This approach provides the certainty that surgical intervention is necessary on a functional basis and is arguably the most accurate method for determining which kidneys are in need of surgical intervention. However, it has the significant drawback that by the time surgical intervention is instituted, a certain amount of renal functional deterioration has already occurred, and this functional loss may be irreversible. It is on this basis that percutaneous pressure-flow studies can provide an attractive alternative strategy for detecting which kidneys are in need of surgical intervention. A positive percutaneous pressure-flow study demonstrates the presence of excessively high resistance to urine flow in the collecting system and a tendency to develop excessively high RPP. These parameters demonstrate significant obstruction on a physiologic basis. Although it is as yet incompletely determined whether these physiologically significant changes will ultimately lead to deterioration in renal function if the obstruction remains uncorrected, there are accumulating experimental and clinical data that such a correlation exists. Evidence for this correlation includes the detrimental effects of elevated RPP on renal function (see Pathophysiology) and our current experience of a 100% negative predictive value for the diuresis pressure-flow study. Pending further validation, percutaneous pressure-flow study holds the promise of being able to select kidneys that are in need of surgical correction of obstruction before renal deterioration occurs, thus maximizing long-term renal function by the timely institution of surgical therapy.

The marked discrepancy noted between furosemide renal scan $T_{½}$ values and diuresis pressure-flow study results warrants discussion in the context of clinical utility. The reason for the discrepancy is not so much that one test is correct and the other faulty; rather, the two tests measure entirely different physical parameters. On the surface, they appear similar in that they both utilize intravenous fluid hydration, the induction of diuresis by intravenous furosemide administration, and a bladder catheter. However, the furosemide renal scan $T_{½}$ provides a measure of the rapidity of clearance of radioisotope from the collecting system, which is essentially a semiquantitative measure of the rate of flow across the suspected site of obstruction. The diuresis pressure-flow study peak RPP, on the other hand, reflects the resistance of the collecting system under a high-flow state induced by furosemide and also reveals whether the renal unit is in a state of active compensation in response to physiologically significant obstruction. Therefore, the lack of correlation between furosemide renal scan $T_{½}$ values and diuresis pressure-flow study peak RPPs simply indicates that the rate of urine flow across the suspected site of obstruction bears no correlation with the resistance of the collecting system or the tendency for RPP to elevate to detrimental levels.

There is currently no proof that the flow rate of urine across an obstructive site is predictive of future functional status, whereas excessively high resistance of the collecting system or high RPP has been shown to result in renal functional deterioration. Therefore, we believe that the furosemide renal scan $T_{½}$ should be interpreted with these considerations in mind and should play, at best, a minor role in determining whether surgical correction is necessary. Conversely, we believe that the percutaneous pressure-flow study results are highly relevant in the detection of physiologically significant obstruction and can be relied on in determining whether surgical or observational management is most appropriate.

Last, it is important to recognize that hydronephrosis is a dynamic condition in the pediatric patient. No matter how accurate a particular test may be, it can provide only a single evaluation frozen in time. Significant improvement or deterioration can occur in an unpredictable fashion as the child grows. Regardless of how sophisticated diagnostic tests may become, diligent longitudinal clinical follow-up with serial evaluations remains an irreplaceable aspect of the management of pediatric hydronephrosis.

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CHAPTER 11

MAGNETIC RESONANCE IMAGING OF THE PEDIATRIC URINARY TRACT

Andrew J. Kirsch and J. Damien Grattan-Smith

Magnetic resonance imaging (MRI) is emerging as a powerful diagnostic tool for imaging of the pediatric genitourinary tract and will probably become the primary tool for comprehensive evaluation of urinary tract anomalies. Despite their widespread use, ultrasonography, renal scintigraphy, computed tomography (CT), and intravenous urography (IVU) have inherent shortcomings. Ultrasonography is an accurate and cost-effective method of diagnosing urinary tract dilatation, but it is operator dependent, does not allow visualization of the middle and lower ureter, and does not provide functional information about the kidneys. Renal scintigraphy provides functional assessment of the kidneys but supplies little anatomic information. Although CT and IVU provide both anatomic and qualitative function evaluation, they rely on both ionizing radiation and nephrotoxic contrast agents. Voiding cystourethrography (VCUG) provides information regarding vesicoureteral reflux (VUR) and the anatomy of the lower urinary tract. MRI has intrinsically greater spatial and contrast resolution compared with other modalities, and, with the advent of new imaging strategies, it can combine this high spatial and contrast resolution with excellent temporal resolution. The use of intravenous contrast agents such as gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) enables one to assess renal perfusion, concentration, and excretion.

Since 2001, we have developed and refined our protocols for evaluating the urinary tract in children using magnetic resonance urography (MRU).[1-5] In addition to high-resolution anatomic images of the entire urinary tract, functional information about the concentration and excretion abilities of the individual kidneys can be obtained. By scanning dynamically after injection of a contrast agent, the signal changes related to perfusion, concentration, and excretion of the contrast agent can be sequentially evaluated in both the renal cortex and the medulla. Pelvicalyceal and ureteric anatomy is assessed using both T2-weighted and contrast-enhanced images. The functional information obtained routinely includes renal transit time (RTT) calculation, signal intensity versus time curves, differential renal function (DRF) calculation, and estimation of individual kidney glomerular filtration rate (GFR). The improved anatomic and functional information obtained with MRU provides insights into the pathophysiology of urinary tract disorders. As a result, it is likely that MRU will replace renal scintigraphy in the evaluation of renal tract disorders in children in the near future.

PRACTICAL CONSIDERATIONS IN THE STANDARDIZATION OF PEDIATRIC MAGNETIC RESONANCE IMAGING

A standardized MRI protocol is of paramount importance to ensure consistency and reproducibility across studies and institutions. As is standard for the "well-tempered" renogram,[6] special attention should be given to consistent program parameters, pre-procedure hydration, dosage and timing of contrast, and diuretic administration. All infants and almost all children up to the age of 7 years will require sedation for MRU.

MAGNETIC RESONANCE UROGRAPHY: TECHNIQUE

The imaging protocols used for our clinical studies consist of conventional T1- and T2-weighted sequences obtained before contrast administration and dynamic three-dimensional gradient-echo sequences obtained after contrast administration (Fig. 11-1).[1-3,5] All children are hydrated before the procedure with an intravenous infusion of lactated Ringer's solution; for sedated children, the volume infused is calculated to replace the NPO deficit; otherwise, the volume is calculated using a guideline of 10 mL/kg. Appropriate hydration is crucial to minimize susceptibility artifacts from concentrated gadolinium and to promote reproducible measurements of renal function. Almost all children younger than 7 years of age require sedation for the examination. A bladder catheter is placed to eliminate the possibility of reflux and to ensure free drainage of the bladder. The patient is placed in a supine position on the bed of a 1.5-T scanner fitted with 30 mT/m gradient coils. Signal reception is via the spine coil in conjunction with one or two multi-element phased arrays placed anteriorly on the abdomen, all radiofrequency transmission is via the body coil. Once the patient is positioned in the scanner, scout images are acquired to determine both the positioning of the kidneys and bladder and the combination of coil elements required to optimize the signal-to-noise ratio (SNR) for these anatomic structures. The T2-weighted images are particularly useful to define the anatomy of nonfunctioning or poorly functioning systems (Fig. 11-2). These systems are generally associated with marked hydronephrosis or cystic changes, and heavily T2-weighted images are able to delineate the anatomy even if little contrast excretion occurs.

The dynamic series starts approximately 15 minutes after the injection of furosemide, which coincides with the maximum effect of the furosemide.[7] A bolus injection of 0.1 mmol/kg Gd-DTPA (Magnevist; Berlex Laboratories, Wayne, NJ) is injected slowly using a power injector over 20-60 seconds during the acquisition of the fourth dynamic image. Each time point of the dynamic sequence consists of 36 slices, with the outer three slices on each side being discarded, to limit variations in the flip angle related to the slice profile and also to limit wraparound artefacts. Parallel imaging may be used to reduce the acquisition time per volume. The scans are acquired contiguously for the first 3 minutes, after which intervals of progressively increasing duration are inserted between the scans until the scans are performed at 1-minute intervals. For each volume acquisition, a maximum intensity projection (MIP) of the whole volume is automatically generated. The images and MIPs are reconstructed and viewed during the dynamic scanning, and, if both ureters were clearly visualized 10 minutes after the injection of contrast

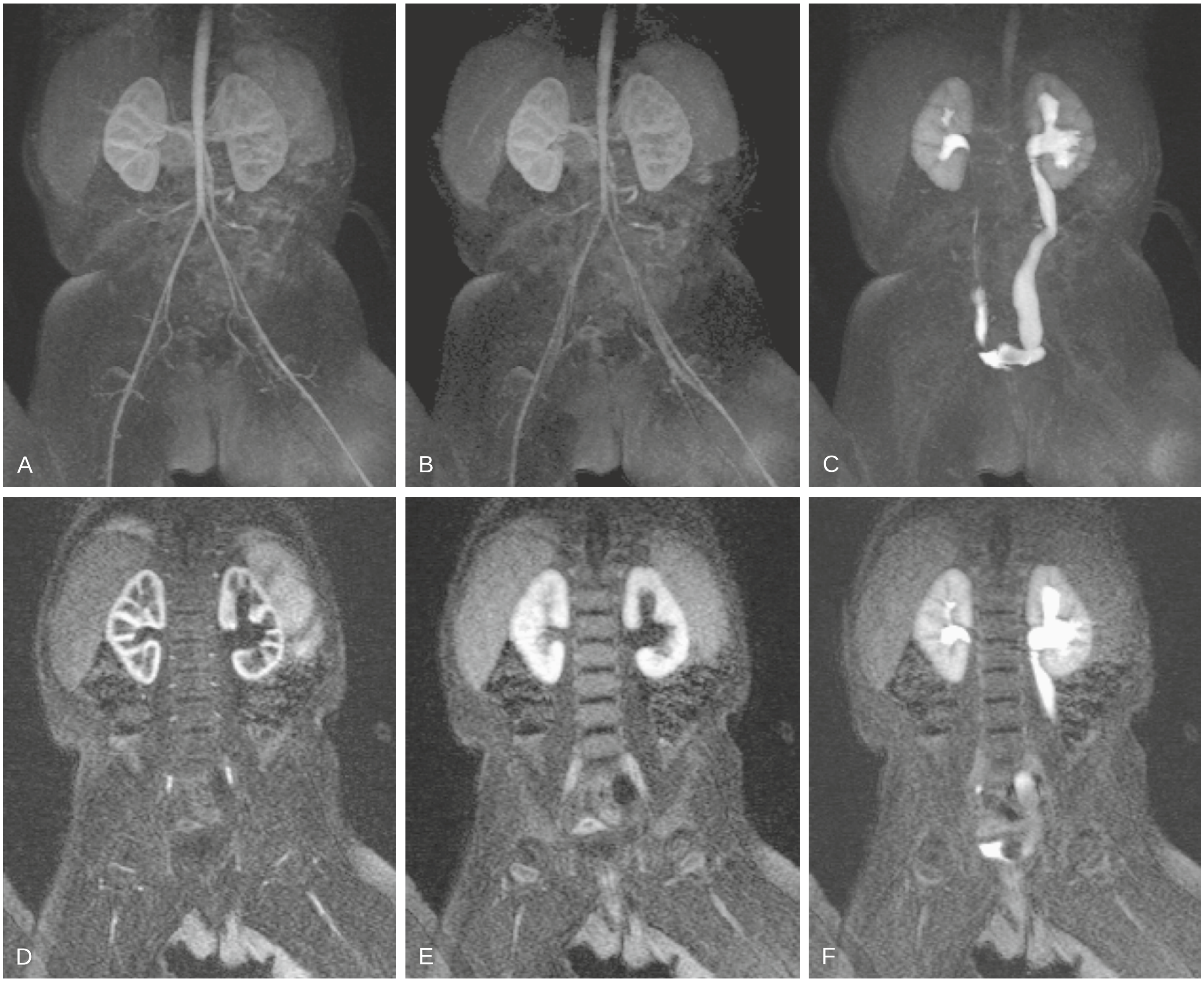

Figure 11-1 Three-dimensional gradient echo sequences. Magnetic resonance urogram in a 3-month-old boy with antenatal hydronephrosis and nonobstructive megaureter. Images **A** through **C** are maximum intensity projections derived from three separate time points; **D** through **F** show the same slice from each of the three volume acquisitions. **A** and **D** show the cortical phase; **B** and **E** were acquired 60 seconds later and demonstrate enhancement of both cortex and medulla, with the signal intensity of the medulla exceeding that of the cortex. **C** and **F** were acquired 120 seconds after the vascular phase and show excretion into the calyces, renal pelves, and ureters.

medium, no further dynamic series are acquired. Otherwise, the acquisition of dynamic images is continued for a further 5-minutes at 1-minute intervals. After the completion of the dynamic series, sagittal, axial, and coronal three-dimensional images with high spatial resolution are acquired for the purpose of generating a postcontrast MIP (Fig. 11-3). The total imaging time for nonobstructed patients is typically 45 minutes; for those with poorly draining kidneys, the imaging time is typically 1 hour. The delayed high-resolution anatomic images are particularly valuable in the evaluation of congenital malformations, including ureteric strictures and ectopic ureteric insertion, as well as complex postoperative anatomy.

The three-dimensional volume data sets cover the full extent of both kidneys, and the uptake of the contrast agent in each kidney can be monitored volumetrically. We make the assumption that voxels represent either functional or nonfunctional tissue and that, by summing the voxels that show a significant uptake of contrast, one can calculate the functional volume of each kidney and hence the DRF. The dynamic series are visually inspected to determine the volume in which contrast is first seen in the collecting system of each kidney; the volume before that one is then used for the calculation of the functional volume of each kidney (Fig. 11-4). In this way, possible differences between the two kidneys are taken into account, and it is not necessary to assume a particular time point, or range of times, for the calculation. In previous studies, several authors showed that calculation of the DRF based on the volume of enhancing renal tissue agrees well with the DRF calculation based on renal scintigraphy.[1,5,8] The volume of functioning tissue has also been shown to be well correlated with creatinine clearance rates.[9] With the dose of contrast and the pulse sequence parameters used, segmentation of the kidneys at this homogeneous enhancement phase is straightforward and can be performed using semiautomatic segmentation. In the evaluation of duplex kidneys, MRU can

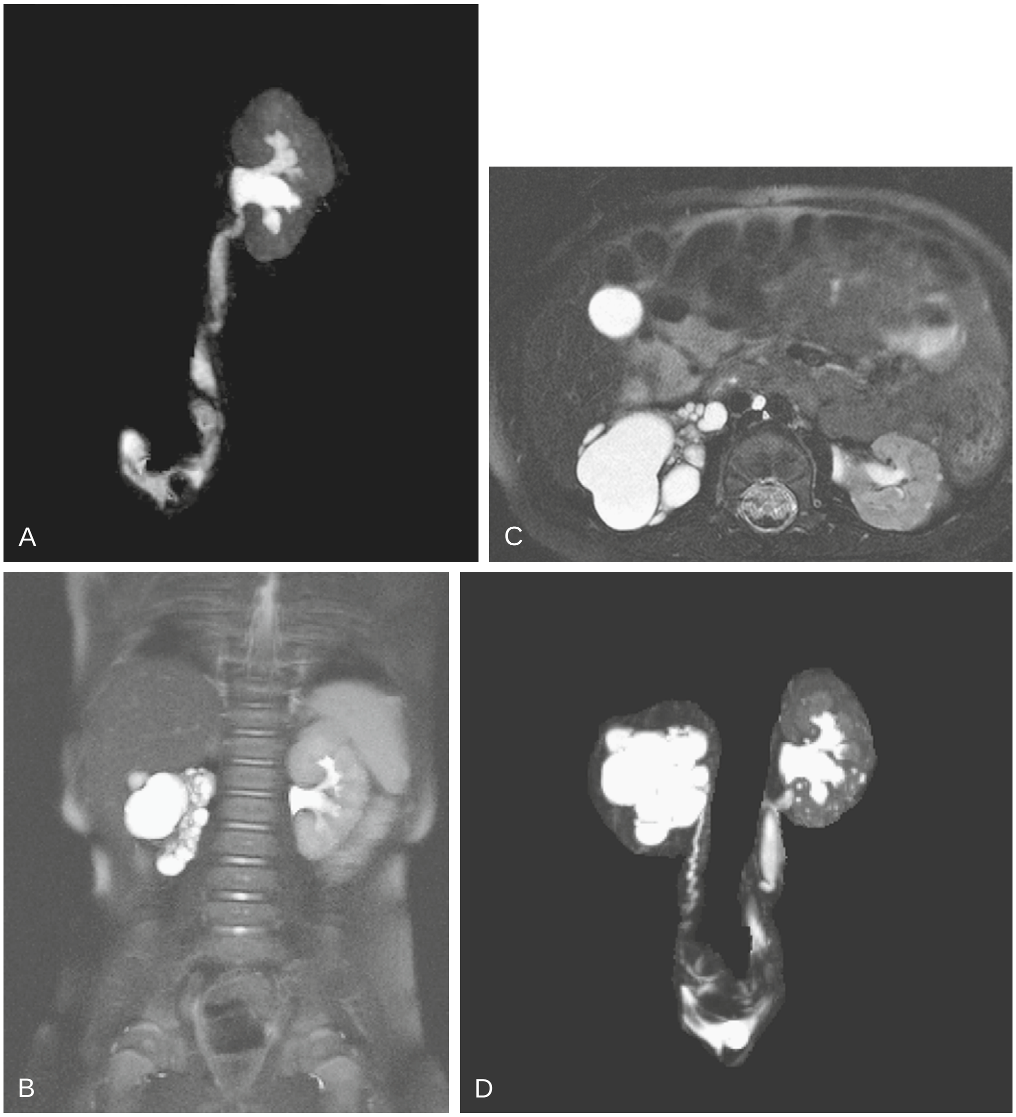

Figure 11-2 Magnetic resonance urograms of renal dysplasia. **A,** T1-weighted contrast-enhanced images demonstrate nonfunction of the right multicystic dysplastic kidney. Differential function is 100% on the left. **B,** Coronal T2-weighted image again demonstrates right multicystic dysplastic kidneys and apparently normal left kidney. **C,** Axial high resolution T2-weighted images show multiple cysts of varying sizes in the right kidney with no normal parenchyma. The left kidney is also dysplastic with multiple, small peripheral cysts and loss of the normal corticomedullary differentiation. **D,** T2-weighted maximum intensity projection (MIP) shows multicystic dyplastic kidney as well as small caliber proximal ureter. Multiple cysts are more apparent in the left kidney on MIP image.

separate the boundaries between the upper- and lower-pole moieties by delineating the column of cortex separating the upper and lower poles, so that the relative contributions of the upper and lower poles can be estimated.

Our initial approach to analyzing the dynamic data was to segment the cortex and medulla and obtain time-intensity curves for each of these regions.[1,2,4] The resulting signal-versus-time curves were then converted to relative signal-versus-time curves by calculating $(S_t - S_0)/S_0$, where S_t is the signal at a given time point and S_0 is the mean precontrast signal, for each time point. The relative signal has a linear relationship with contrast agent concentration over a limited range of concentrations and compensates for spatial variations in the background signal, facilitating comparison of the two kidneys.[2] Several characteristic features are seen in the curves. The cortex shows an initial peak caused by concentrated contrast material in the vasculature, and a subsequent peak is seen at a later time point due to the arrival of contrast in the distal convoluted tubules.[10] The medullary curves show a single peak (designated LH) corresponding to contrast in the loop of Henle. Although it is possible to routinely generate separate signal intensity-versus- time curves for the cortex and medulla, the process is time-consuming, and in most clinical cases this information can be assessed visually directly from the images (Fig. 11-5).

DETERMINATION OF DIFFERENTIAL RENAL FUNCTION AND SINGLE-KIDNEY GLOMERULAR FILTRATION INDEX

The most widely used nonimaging clinical test of renal function is to measure the serum creatinine level and determine creatinine clearance. However, this test is a relatively insensitive measure of decreased GFR and measures only global, rather than single-kidney, function. Several groups

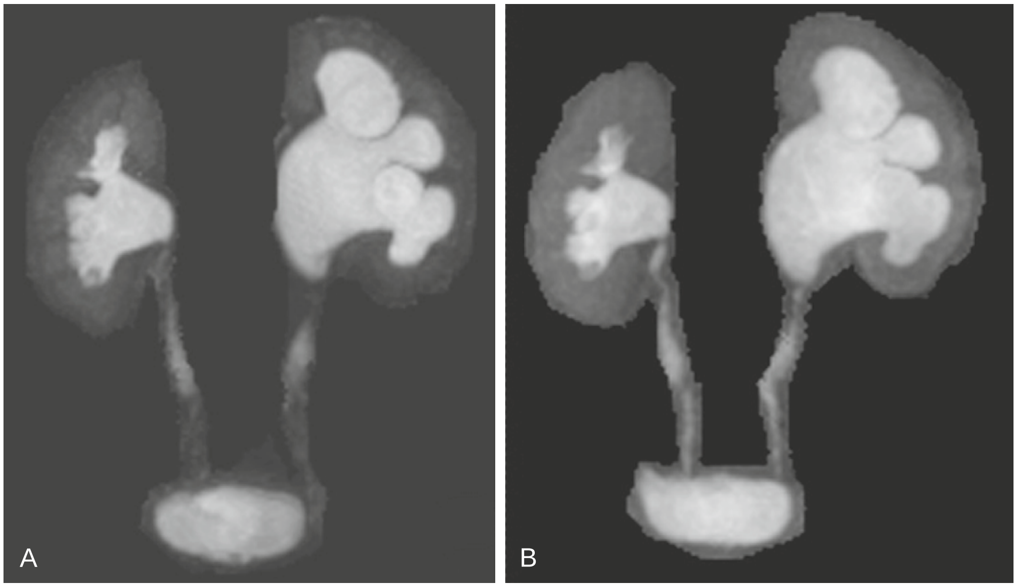

Figure 11-3 A 6-month-old boy with ureteropelvic junction (UPJ) obstruction. **A,** T2-weighted maximum intensity projection (MIP) shows morphologic UPJ on the left with transition to a normal-sized ureter. The T2-weighted images highlight static fluid collections and are particularly useful in poorly functioning or markedly hydronephrotic systems. **B,** Postcontrast MIP again demonstrates typical morphologic features of UPJ obstruction. The postcontrast images are T1 weighted, and the signal intensity is determined by the excreted contrast agent. The postcontrast MIPs tend to have greater spatial resolution.

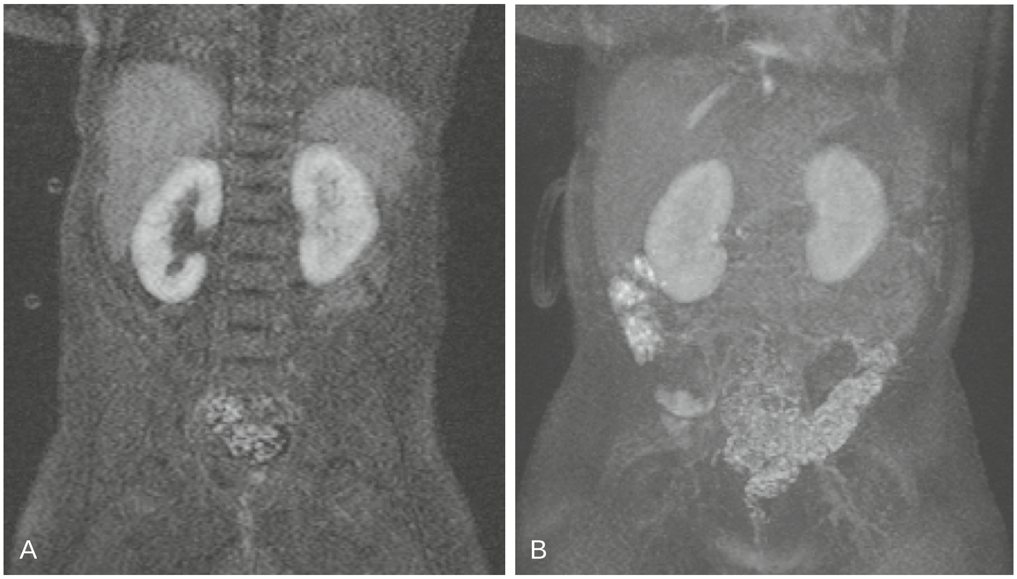

Figure 11-4 Calculation of differential renal function (DRF) using renal volumes. **A,** Medullary phase source image at the time point used for calculation of DRF. The time point chosen occurs when there is symmetric enhancement of the renal cortex and medulla immediately before excretion of contrast into the collecting systems. **B,** In the maximum intensity projection image, the enhancement of the kidney allows easy separation from background tissues, so that the volume calculation can be generated semiautomatically. The DRF was calculated to be 51% on the left and 49% on the right.

have applied the methods developed for nuclear medicine to dynamic MRI data acquired in conjunction with an injection of the contrast agent Gd-DTPA.[11,12]

To estimate the GFR, we use the Rutland-Patlak technique, which is based on a two-compartment model with unilateral flow of tracer from the first compartment (vasculature) into the second compartment (nephrons).[13-15] The relative signal-versus-time curves from the aorta and kidney can be used to generate a Patlak plot and thereby estimate the GFR. The value derived from the slope of the Patlak plot is probably best regarded as a GFR index rather than an absolute measure of the GFR. Despite these problems, the GFR values obtained from adult volunteers by the Patlak method are in good agreement with those obtained by reference methods.[11,16] When the Patlak DRF is calculated, such effects are assumed to be common to both kidneys and can therefore be ignored (Fig. 11-6).

For each patient, the key features derived from MRU include calculation of DRF (both volumetric and Patlak), relative signal-versus-time curves for each kidney and the aorta, the individual kidney GFR index of each kidney, concentration and excretion from each compartment, RTT, and overall anatomic diagnosis. It is important to understand

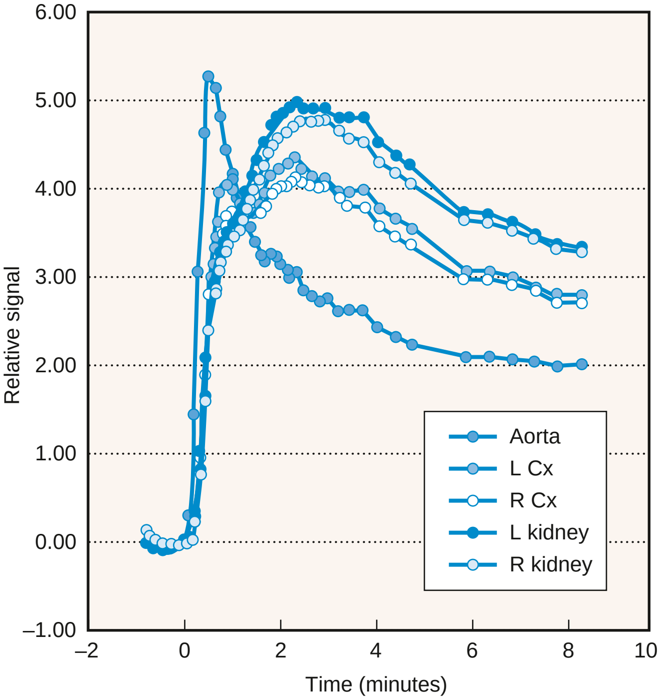

Figure 11-5 Relative signal intensity-versus-time curve showing salient features. Note the symmetric cortical curves with well-defined vascular and distal convoluted tubular peaks and the peak related to enhancement of the medulla with concentration in the loop of Henle. The corticomedullary crossover point is symmetric, indicating equivalent intratubular pressures. Mild asymmetry of the medullary peaks is considered within normal limits. Cx, cortex; L, left; R, right.

that we now have two methods to determine the DRF: one based on volume and one based on the individual kidney GFR as determined by the Patlak plot. In most cases, these values are similar; if there is a difference in the DRF as determined by volume and that determined by the Patlak plot, a change in glomerular hemodynamics is implied, and this may ultimately provide information about which kidneys will benefit from surgery. We have begun to use Patlak indices of GFR to compare the functional contribution of each kidney with overall renal function.[17]

DETERMINATION OF RENAL DRAINAGE

Nuclear diuretic renal scintigraphy (DRS) has long been the study of choice to rule out obstruction and determine DRF in children with upper urinary tract dilatation. However, MRU has been shown to be a useful tool for distinguishing an obstructed dilated system from an unobstructed one, even when technetium 99m-labeled mercaptoacetyltriglycine (^{99m}Tc-MAG3) renography results are compromised by reduced renal uptake in the affected kidney.[18] The advantage of MRU is that, in addition to providing anatomic information exceeding that provided by ultrasound, computer-assisted postprocessing techniques can be employed to quantify objectively the function and degree of obstruction.

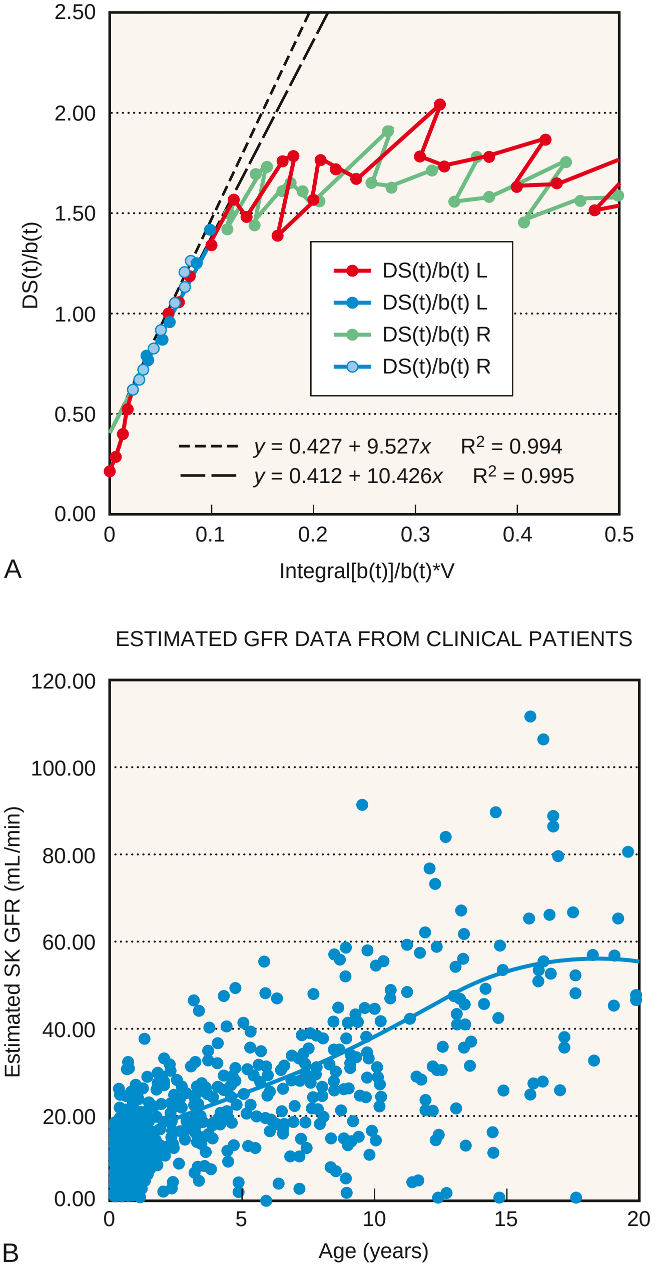

Figure 11-6 **A,** The Patlak plot is used as an index of the individual kidney glomerular filtration rate (GFR). The slope of each plot reflects the GFR of each kidney (9.5 mL/min on the left and 10.4 mL/min on the right). The Y intercept represents the fractional blood volume of each kidney. When corrected for body surface area, these values become 42 and 46 mL/min, respectively, so that the total GFR index is 88 mL/min. **B,** Plot of GFR based on the Patlak plot versus age in our clinical population. SK, single kidney.

We have used MRU to evaluate hydronephrosis and obstruction by calculating the RTT, which is defined as the time it takes for the contrast agent to pass from the renal cortex to the ureter below the lower pole of the kidney.[3] If the RTT is less than 245 seconds, the system is considered nonobstructive. If the RTT is greater than 490 seconds, the system is probably obstructed. RTT times between 245 and 490 seconds are considered equivocal and are managed conservatively with close follow-up to ensure that renal function is stable. Calculation of the RTT from the images is relatively straightforward, because each individual volume acquisition is time-stamped: the time at which the cortex first enhances and the time at which contrast is first identified in the ureter can be determined visually from the images. The RTT is simply the difference between these two time points. Our experience with RTT has emphasized that obstruction represents a spectrum of impairment to urinary flow, and the progressive renal damage is caused by complex alterations in glomerular hemodynamics and tubular function.[3,19,20]

Although we have shown that RTT is similar to DRS for categorizing dilated systems, it still does not prospectively identify kidneys that will lose function if left untreated. The clinical situation that combines hydroureteronephrosis with poor renal function is also problematic for MRU (Fig. 11-7). If there has been significant loss of renal parenchyma and little urine is being produced, the RTT is of limited value in evaluating the presence of superimposed obstruction.

In our prospective study[5] at Children's Healthcare of Atlanta comparing ultrasonography, DRS, and MRU in the evaluation of hydronephrosis, MRU provided equivalent information about renal function but superior information regarding morphology in a single study without ionizing radiation. Compared with DRS, MRU had a higher sensitivity (100% versus 96%), a higher positive predictive value (86% versus 76%), a better negative predictive value (100% versus 90%), and better diagnostic efficiency (90% versus 79%).[1]

Indeed, the availability of MRU has influenced our diagnostic strategy for the evaluation of pediatric hydronephrosis. We have adapted our diagnostic algorithm to include MRU and currently use this modality in the evaluation of many patients with Society of Fetal Urology (SFU) grade III and most of those with grade IV hydronephrosis on confirmatory sonography. We have used MRU to evaluate more than 1500 children with hydronephrosis. MRU has been found to be particularly useful for the diagnosis and evaluation of a wide range of obstructive urinary tract anomalies, including ureteropelvic junction (UPJ) (Fig. 11-8) and ureterovesical junction obstruction, megaureters, and ectopic ureters. Furthermore, we have used the technique to evaluate the surgical results of pyeloplasty.[17] After correction of UPJ obstruction, DRF, RTT, and Patlak scores (GFR index) improved significantly, further validating the use of MRU parameters for predicting obstruction.

Although MRI has been dismissed as a poor procedure for the diagnosis of urolithiasis, primarily because of the radiolucency of calculi, excretory MRU has demonstrated sensitivity between 90% and 100% in patients with stones.[21-23] In addition to excellent anatomic characterization of the parenchyma and collecting system, the unique ability of MRU to provide quantitative functional information such as DRF, RTT, and GFR (Patlak score) makes it the most comprehensive of the currently available diagnostic procedures in the assessment of upper urinary tract dilatation.

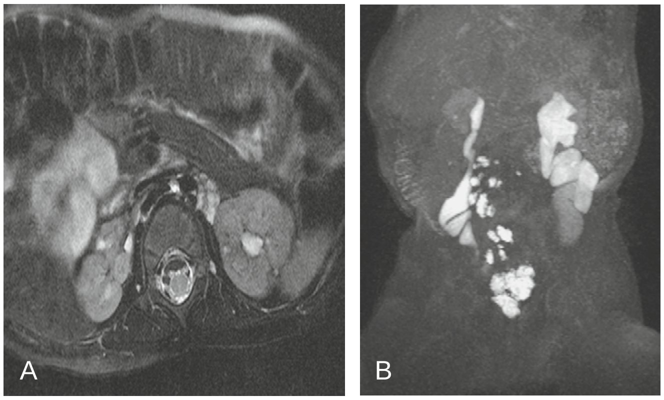

Figure 11-7 **A,** High-resolution, T2-weighted image shows poor corticomedullary differentiation with parenchymal scarring in the right kidney. **B,** Delayed coronal contrast–enhanced maximum intensity projection shows dilated ectatic ureters bilaterally with dysmorphic calyceal systems bilaterally, typical for prune-belly syndrome.

CLINICAL APPLICATIONS OF MAGNETIC RESONANCE UROGRAPHY

MRU has proved to be a model investigative tool in children with uncertain results from conventional imaging studies. The wide range and complexity of anatomic variants encountered in pediatric urology have traditionally required an amalgamation of studies to obtain adequate visualization, often employing ionizing radiation. Doppler ultrasound, IVU, VCUG, nuclear scintigraphy, genitograms, and retrograde urography often do not provide a comprehensive picture of the complex anatomy because of their intrinsic limitations. MRU has become an increasingly popular tool for the evaluation of complex genitourinary anatomy. MRU provides not only a three-dimensional evaluation of the urinary tract but also an assessment of renal function that can aid management decisions. MRU has become the preferred imaging procedure for the identification of ureteral ectopia (Fig. 11-9).[24-27] Not only has MRU proved to be superior to ultrasound and IVU in the evaluation of the distal ectopic ureter, but often it has been the only procedure that can identify and demonstrate

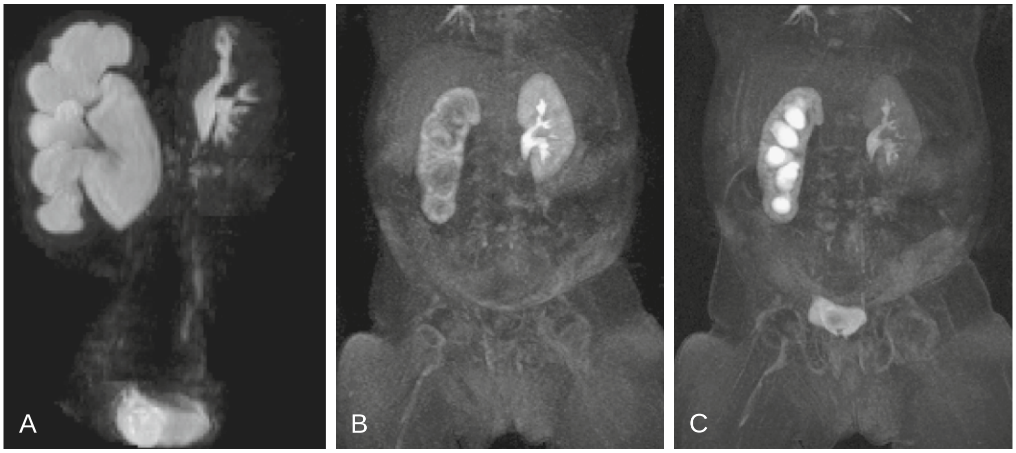

Figure 11-8 Ureteropelvic junction obstruction with delayed and dense nephrogram. **A,** T2-weighted maximum intensity projection (MIP) showing marked hydronephrosis with transition at ureteropelvic junction. **B,** T1-weighted MIP image 5 minutes after contrast administration showing delayed dense nephrogram on the right. **C,** T1-weighted MIP image 15 minutes after contrast administration showing contrast into the calyceal system but not yet filling the renal pelvis.

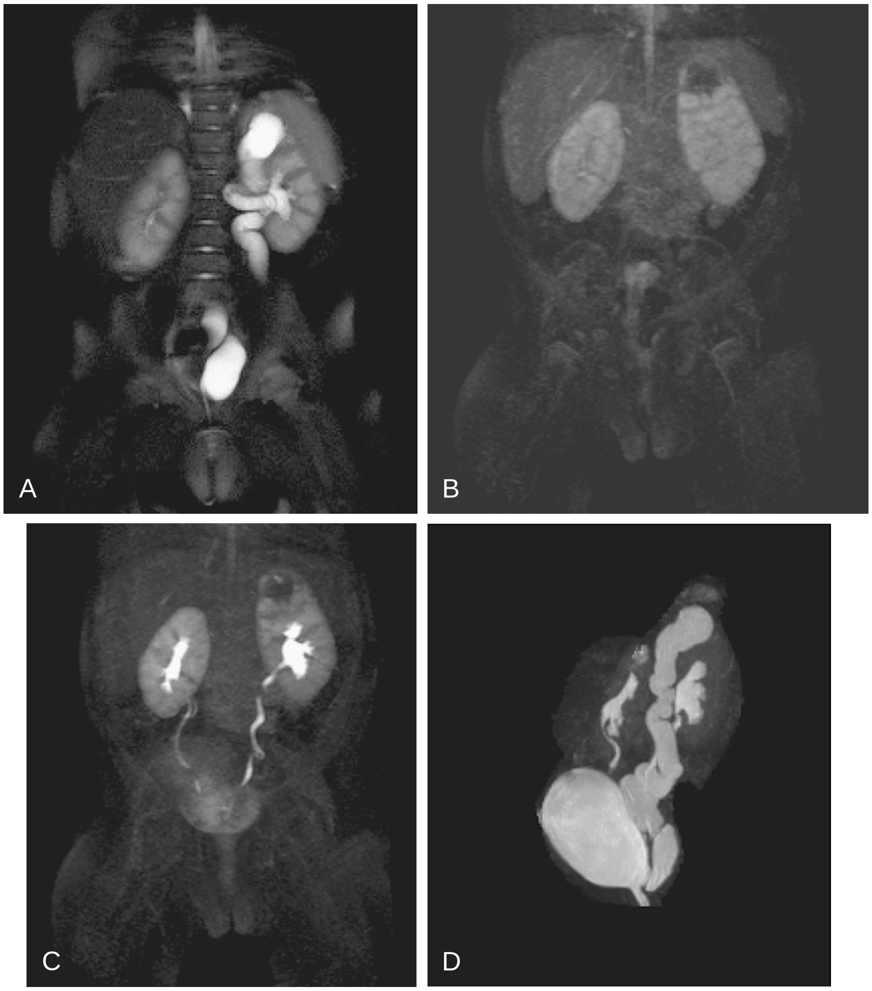

Figure 11-9 Duplex left kidney with ectopic upper-pole ureter to urethra. **A,** Coronal T2-weighted image showing duplex left kidney with hydroureteronephrosis of the upper pole. **B,** T1-weighted maximum intensity projection (MIP) image 1 minute after contrast administration showing normal parenchymal enhancement of the right kidney and left lower pole. There is little enhancement of the upper pole on the left. **C,** T1-weighted MIP image 10 minutes after contrast administration showing minimal excretion into the upper pole moiety. Note spiral appearance of lower pole ureter as it intertwines with dilated upper pole ureter. **D,** Oblique T2-weighted image showing the insertion of the upper pole ureter ectopically into the urethra.

the ureter in poorly functioning moieties.[28] Additionally, Riccabona and colleagues[29,30] demonstrated MRU to be superior to conventional imaging procedures in the assessment of children with a suspected single functional kidney, through better characterization of the contralateral dysplastic or ectopic moiety.

Congenital Renal Malformations

Anomalies of renal position and rotation are well demonstrated by the high-resolution anatomic images. Horseshoe and ectopic kidneys can be easily separated from the background and overlying tissues. Ectopic kidneys with UPJ obstruction can readily be evaluated. Hypoplastic kidneys associated with ureteric ectopia and supernumerary kidneys, which have been difficult to demonstrate with other imaging modalities, can usually be demonstrated even if there is minimal renal function. Supernumerary kidneys, although rare, can be visualized only on MRU or CT scans.

MRU has been used as an adjunct in the evaluation of renal cystic disease, often being employed when the diagnosis is unclear (Fig. 11-10). Kern and associates[31] demonstrated the use of MRU in the confirmation of autosomal recessive polycystic kidney disease and the characterization of potential hepatic involvement.

The various forms of renal dysplasia include multicystic dysplastic kidneys (MCDK), cystic obstructive dysplasia, hypodysplasia, and solid renal dysplasias.[30] We retrospectively reviewed 67 infants born with significant antenatally diagnosed hydronephrosis who underwent MRU in the first 6 months of life. MRU findings of renal dysgenesis were seen in 24 renal units (28%) and included loss of corticomedullary differentiation with preserved parenchyma, renal cystic changes distinct from MCDK, solid renal dysplasia, hypoplasia, dysmorphic calyces, and impaired concentrating ability.[32]

MRU is excellent for demonstrating anomalies of the upper and lower tracts such as ureteroceles (Fig. 11-11) and seminal vesicle cysts associated with cystic and dysplastic kidneys. Anomalous calyceal development is better defined on MRU than on other imaging studies.

Evaluation of Hydronephrosis

The most common indication for MRU has been the evaluation of pediatric hydronephrosis. In children, hydronephrosis is usually a result of chronic partial obstruction, typically

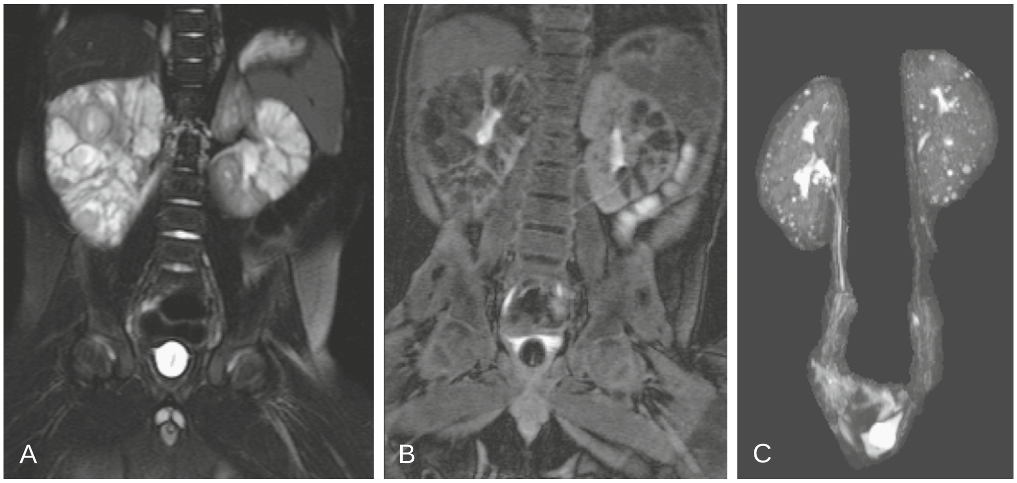

Figure 11-10 T2-weighted **(A)** and postcontrast **(B)** magnetic resonance urograms in a child with autosomal dominant polycystic kidney disease. **C,** Multiple cysts associated with tuberous sclerosis complex.

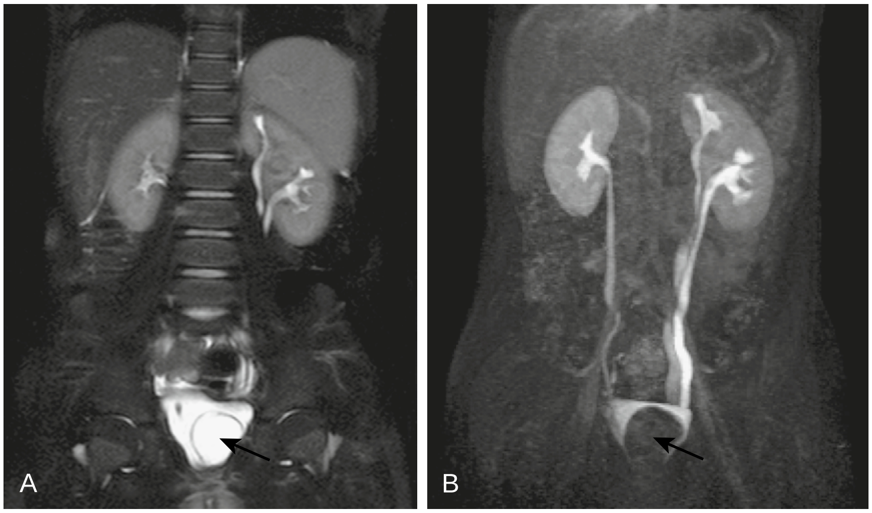

Figure 11-11 Duplex left kidney with large intravesical ureterocele. **A**, Coronal T2-weighted image showing fluid-filled ureterocele (*arrow*) in the bladder. **B**, T1-weighted maximum intensity projection image 10 minutes after contrast administration showing duplex left kidney with contrast in both ureters as well as filling defect in bladder representing the urine-filled ureterocele (*arrow*).

related to UPJ obstruction or obstructive megaureter. The consequences of the obstruction not only are dependent on the degree of obstruction but occur secondarily to a complex syndrome, resulting in alterations of both glomerular hemodynamics and tubular function, that is caused by the interactions of a variety of vasoactive factors and cytokines.[19,20]

All hydronephrotic systems are obstructed to some degree, and we need to develop sensitive measures to detect early renal functional deterioration. Any attempt to separate obstructed from nonobstructed kidneys as distinct entities is artificial and unrealistic.[3,33] The ultimate goal in the management of obstruction is preservation of renal function through improved urinary drainage. Currently, there is no imaging modality that can accurately assess the degree of obstruction and hence identify which kidneys are at risk for a progressive loss of renal function. MRU may provide new information that will further our understanding of obstructive uropathy from a physiologic and molecular standpoint.

Evaluation of Ureteral Anomalies

The ureters are reliably identified in most children by MRU. The ability to delineate the ureteric anatomy has allowed us to confidently make the diagnosis of midureteric stricture. The combination of transition in ureteric caliber and delayed excretion are the key features in the diagnosis of ureteric stricture. Ureteric anatomy cannot be accurately evaluated by ultrasonography or renal scintigraphy. Although midureteric stricture has been considered a rare anomaly in children, it can be readily diagnosed by MRU and has probably been underdiagnosed by traditional modalities.[34] Complete or partially duplicated ureters (e.g., Y ureters) are easily identified on MRU by evaluating the T1- and T2-weighted images.

The distal ureteric anatomy is also well demonstrated by MRU.[25] Ectopic ureteric insertion, either in single systems or in combination with duplex systems, can usually be visualized on the delayed postcontrast images or on the T2-weighted images in markedly dilated or poorly functioning systems. The differentiation of obstructed from nonobstructed megaureter is made on the basis of RTT. In many cases, follow-up studies of primary megaureter with equivocal RTT show elongation and lengthening of the ureter with improvement in RTT. MRU can also demonstrate both simple and ectopic ureteroceles.

Evaluation of Ureteropelvic Junction Obstruction and Megaureter

At Children's Healthcare of Atlanta, we have examined the use of MRU for functional and anatomic evaluation of UPJ obstruction and megaureters.[1-5,17,32,35] MRU is our study of choice for moderate to severe hydronephrosis. Using the combination of RTT, DRF, and various characteristics of the time-intensity curves, we were able to demonstrate the classification of obstructed, equivocal, and nonobstructed renal units. Additionally, the anatomic resolution allowed us to visualize characteristics associated with obstruction. Obstructed systems had more marked hydronephrosis, more extensive medullary atrophy, more fluid levels, and more swirling of contrast material.

Dynamic, contrast-enhanced MRU provides comprehensive information in a single study to guide management in children with megaureters (Fig. 11-12) and for preoperative identification of ectopic ureteral insertions. Serial MRUs showing preserved function and stable RTT support nonoperative management. Functional deterioration, nonfunction, or worsening RTT supports operative management.

Assessment of Vascular Malformations and Anomalies

The early vascular phase of the MRU provides a detailed evaluation of the vascular system. Anomalies of the renal vessels (e.g., multiple renal arteries, crossing vessels) are easily identified (Fig. 11-13). The presence of such anomalies does not necessarily implicate the vessels as the cause of obstruction, however. In addition, high-insertion ureter may lead to intermittent obstruction and may not be seen on MRU when obstruction is absent.

Vesicoureteral Reflux

VCUG has long been the established gold standard for the detection of VUR. Despite its ability to provide excellent visualization of the entire urethra and to assess the presence and grade of VUR, conventional VCUG involves direct radiation

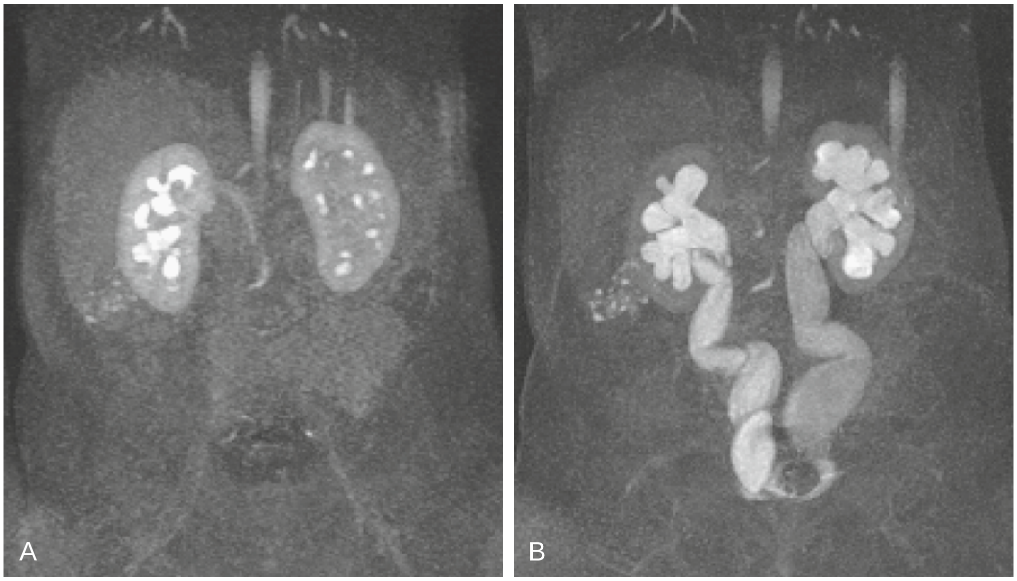

Figure 11-12 Bilateral primary obstructing megaureters seen on T1-weighted **(A)** and T2-weighted **(B)** magnetic resonance images.

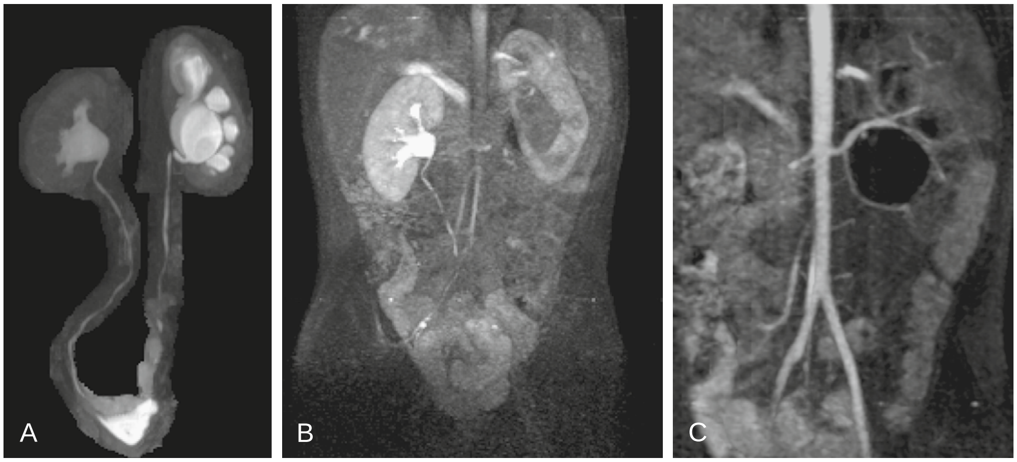

Figure 11-13 Images of left ureteropelvic junction obstruction on T2-weighted magnetic resonance urogram **(A),** showing poor excretion on T1-weighted images **(B)** and associated with a crossing vessel **(C).**

exposure to the gonads. Magnetic resonance voiding cystourethrography (MRVCU) was first described in 1992 but did not become a potential alternative until the advent of near–real-time magnetic resonance fluoroscopy.[36] MRVCU is composed of T1-weighted images of the entire genitourinary tract obtained before the transurethral administration of Gd-DTPA, as well as images obtained during and after micturition. Rodriguez and coworkers[37] performed MRVCU before excretory MRU and demonstrated reflux in four of five children with known VUR. In another study[38] using conventional VCUG as the standard reference, MRVCU was found to have a sensitivity of 76% and a specificity of 90% in the detection of VUR. In addition, renal scarring was detected in 13 of 17 kidneys confirmed by nuclear scintigraphy. Therefore, MRVCU allows for an accurate determination of VUR and reflux nephropathy. Limitations may include difficulty voiding in the supine position for some patients and incomplete voiding in some infants and young children due to sedation. Although the procedure is technically feasible, it seems unlikely that MRVCU will gain widespread acceptance.

Pyelonephritis and Renal Scarring

Although the diagnosis of pyelonephritis is based on the clinical constellation of fever, flank pain, and urinary tract infection (UTI), its diagnosis in children and infants is often difficult. Until now, CT and nuclear scintigraphy have been used to confirm the diagnosis of suspected pyelonephritis. CT is used sparingly because of the exposure to ionizing radiation and intravenous contrast. Nuclear scintigraphy, primarily dimercaptosuccinic acid (DMSA) scanning, has become the gold standard in the radiologic evaluation of pyelonephritis. However, DMSA scanning employs ionizing radiation, provides limited anatomic resolution, and poses difficulty in differentiating between acute pyelonephritic inflammation and renal scarring (both appear as photopenic areas on DMSA). Gadolinium-enhanced MRI was initially shown in an animal model to diagnose acute pyelonephritis with sensitivity comparable to that of DMSA.[39]

There have been several reports investigating the role of MRU in the evaluation of acute pyelonephritis and renal scarring.[40-42] MRU is equal to and in some cases superior to DMSA renal scintigraphy in the evaluation of both acute pyelonephritis and renal scarring. Initial descriptions used fast pulses of ionizing radiation after contrast administration to demonstrate areas of acute pyelonephritis (increased signal intensity on a background of low signal intensity).[39,41] The normal kidney becomes diffusely low in signal intensity, and areas of pyelonephritis are seen as areas of higher signal intensity. Cortical scars are seen as focal areas of volume loss with deformity of the renal contour. The underlying calyx is often deformed. More recently, the cortical phase of the dynamic postcontrast scan has been used to demonstrate cortical perfusion defects similar to those seen on CT, and this may obviate the need for the longer ionizing radiation sequences in the evaluation of acute pyelonephritis. Evaluation of the parenchymal defects with MRU is relatively straightforward because of the easy differentiation of renal parenchyma from background. One of the distinct advantages of MRU over DMSA scanning is the ability to distinguish acute pyelonephritis from chronic scarring at the time of initial evaluation.

Lonergan and colleagues[41] demonstrated that MRI was superior to DMSA in the diagnosis of pyelonephritis in 37 children with febrile UTI. In addition, the use of MRI in children with suspected pyelonephritis has proved to be cost-effective when compared with DMSA.[42] Therefore, MRI should be considered if the clinical diagnosis of pyelonephritis in a child or infant is unclear.

MRI has the advantage over DMSA in its ability to differentiate between pyelonephritis and renal scarring. On MRI, renal scarring is visualized as an area of focal parenchymal loss. Using DMSA as the reference standard, gadolinium-enhanced T1-weighted MRI was found to have 100% sensitivity and 78% specificity for the detection of renal scarring in a group of 24 children with spina bifida.[43] More recently, however, Kavanagh and associates[40] suggested that a T1-weighted MRI sequence without gadolinium enhancement was sufficient for detection of scarred kidney, demonstrating 77% sensitivity and 87% specificity, compared with 82% and 91%, respectively, for the gadolinium-enhanced scan. We have used the technique of inversion recovery sequencing to differentiate between acute pyelonephritis and renal scarring and believe this to be a highly sensitive modality. In this way, renal scarring may be accurately detected by a rapid (<5 minutes) examination without the use of intravenous contrast or ionizing radiation.

CURRENT LIMITATIONS OF MAGNETIC RESONANCE IMAGING

Despite the advantages of MRI, there are obstacles to its widespread acceptance. Sedation is required in most young children. Standardized equations and values used to determine function and classify drainage have not yet been agreed upon. Larger studies with longer-term follow-up periods are still needed. In this age of cost containment, there are increased costs associated with MRI, and availability remains limited. Although MRI is currently more costly than renal scintigraphy, the comprehensive information obtained may justify its use, especially because it does not expose the patient to ionizing radiation. By reducing the delay in the treatment of disease, the use of MRI may actually reduce overall health care expenses. Furthermore, cost and availability issues are likely to become less important in the future as the use of this modality continues to increase.

CONCLUSION

MRU has the potential to revolutionize the imaging of the urinary tract in children, providing an unprecedented level of anatomic information combined with quantitative functional evaluation of each kidney. MRU can now provide useful assessment of obstructive uropathy and may provide predictive information about which children will benefit from surgery. Further technical developments in the field will produce greater insights into the pathophysiology of not only urologic disorders but also disorders of the kidney itself.

The ability of MRI to provide detailed information regarding anatomy, function, and drainage in a single study without the use of ionizing radiation sets it apart from conventional imaging techniques. As an additional advantage, it can be used in patients with contrast allergy or impaired renal function. MRI is likely to emerge as the modality of choice for children with complex genitourinary pathology, high-grade hydronephrosis, suspected single functional kidney, or diagnostic dilemmas regarding pyelonephritis. Finally, MRI should be thought of as a problem-solving tool to define anatomy and function when conventional methods fall short.

REFERENCES

For complete list of references log onto www.expertconsult.com

SECTION 4

SPECIAL CONSIDERATIONS

CHAPTER 12

GENES, URINARY TRACT DEVELOPMENT, AND HUMAN DISEASE

Adrian S. Woolf

This chapter primarily considers the genetic bases of human urinary tract malformations. Here, the term *urinary tract* will be simply used to refer to the kidneys, ureters, bladder, and urethra. Brief considerations will also be given to the manner by which an altered fetal milieu (e.g., urinary flow impairment, alterations in maternal diet, exposure to teratogens) can alter the expression of genes active in urinary tract development, perhaps in part explaining their ability to perturb the normal program of development. Some urinary tract malformations are associated with congenital anomalies in multiple organ systems; these are called *syndromic* disorders. In most individuals, however, urinary tract malformations occur in isolation (i.e., they are "nonsyndromic"); on occasion, such individuals have a positive family history. For both syndromic and nonsyndromic disease, the last decade has seen advances in defining genetic loci and even mutations of specific genes. This field of study is large and is advancing rapidly, so this chapter is meant to provide the reader with an introduction to the subject and is not intended to be an exhaustive analysis. In the long-term, an understanding of the genetic aspects of human urinary tract malformations could help to unravel the pathogenesis of these disorders and may facilitate the design of genetic screening tests with a view to early diagnosis.

NORMAL DEVELOPMENT OF THE KIDNEY AND LOWER URINARY TRACT

The mammalian kidney derives from two tissue compartments of its mesodermal precursor, the metanephros. These are (1) the ureteric bud, a branch of the mesonephric (wolffian) duct, which itself branches recurrently to form the renal collecting ducts, and (2) the renal mesenchyme, a caudal section of intermediate mesoderm, which undergoes an epithelial transformation via comma- and S-shaped bodies to form nephron components including glomeruli and proximal tubule epithelia.[1-3] The human metanephros appears at 5 weeks of gestation and lies in close proximity to the mesonephros, which is programmed to involute, and the gonadal ridge. The first layer of glomeruli form by 9 weeks' gestation. Branching and nephron formation continue in the outer rim of the kidney, the nephrogenic cortex, until 34 weeks, and further maturation, in the form of growth and differentiation, continues postnatally. The ureteric bud also gives rise to the urothelium of the renal pelvis and the ureter, with the bladder itself forming through interaction of a separate set of (endodermal and mesodermal) tissues.[4] During the second half of human gestation, fetal urine is the main component of amniotic fluid and is required for fetal lung maturation. However, the production of urine before birth is not essential for fetal survival itself, because the placenta effectively performs "hemodialysis."

When these finely tuned processes go wrong, major kidney malformations occur, such as agenesis (absent kidneys), dysplasia (incomplete differentiation, often with metaplastic tissue and cysts), and hypoplasia (too few nephrons). Technically speaking, these are histologic diagnoses, with a hypoplastic kidney being an organ with a significant nephron deficit and a dysplastic kidney being one that is composed, in whole or in part, of undifferentiated and metaplastic tissues. In clinical practice, however, histologic analysis is rarely available, and kidneys are called *hypoplastic* if they are significantly short compared with age-matched normal populations[5-7] yet retain a normal shape and some function. Recent human studies suggest that the range of nephrons found in kidneys from healthy humans is rather large, between 0.5 and 1.5 × 10^6. Adults with essential hypertension have, on average, half as many nephrons as normal (mild renal hypoplasia).[8] *Dysplastic* kidneys range in size from smaller to larger than normal, and they have either reduced or no excretory function; they have loss of corticomedullary differentiation on ultrasonography and may contain cysts which, on occasion, massively distend the organ.[1,9]

Similarly, renal "agenesis" means that the organ never formed; however, the realization that even massive multicystic kidneys can spontaneously involute so that the remnant is beyond the lower limits of radiologic resolution must lead clinicians to question the veracity of such a diagnosis when it is made in later childhood or adulthood.[10,11] The definition of malformation can be extended from gross structural changes to microscopic abnormalities such as "renal tubular dysgenesis," in which proximal tubules form abnormally.[12] Polycystic kidney diseases are excluded from the current discussion because, although some types can affect infants and children,[13] such cysts typically arise after the main steps of kidney development are complete.

As is obvious to clinicians caring for children with kidney malformations, the lower tract is also often affected by anomalies such as refluxing, obstructed or duplicated ureters, and malformed bladders or urethras. Therefore, if mutations are involved in the pathogenesis of both upper and lower tract disease in any one subject, it would not be surprising to find that these same genes are (normally) expressed rather widely throughout the urinary tract. Sometimes, it is convenient to refer to the disease spectrum using the term congenital anomalies of the kidney and urinary tract (CAKUT).[14] With increasing use of fetal ultrasound scanning, more urinary tract malformations are being diagnosed,[15-18] and these disorders account for a significant subset of all antenatal anomalies diagnosed.

The clinical (diagnostic, histopathologic, and prognostic) aspects of these entities are reviewed elsewhere in this book, and the details are not reiterated here. Suffice it to say that any severe bilateral kidney malformation can be associated with oligohydramnios, oligoanuria, and lung hypoplasia, collectively termed the Potter sequence. Furthermore, most young children with chronic renal impairment or severe renal failure requiring dialysis and transplantation have urinary tract malformations.[19,20] With advances in medical care, it is to be expected that more young children with severe kidney malformations will survive into adulthood.[21,22]

CLUES FROM ANIMAL STUDIES OF KIDNEY DEVELOPMENT

The explosion of knowledge regarding the mechanisms of mouse kidney development is relevant to the understanding of human malformations.[2,3] In organ culture work from the middle of the last century, Clifford Grobstein[23] clearly demonstrated that renal mesenchymes and ureteric buds failed to differentiate when cultured in isolation but formed nephrons and collecting ducts when recombined. On account of these mutually inductive interactions, a primary defect of either component must affect the development of its partner. This provides one biologic explanation for the clinical observation that an abnormal ureteric insertion into the bladder is associated with congenital renal parenchymal anomalies[24,25]; on such occasions, an ectopic site of ureteric bud branching from the mesonephric duct is followed by failure of the nascent ureter to (fully) engage the part of the intermediate mesoderm that is destined to form renal mesenchyme.

Using genetically engineered mice and organ culture experiments, researchers have now established that urinary tract development is controlled by diverse molecules, some of which may act as inductive signals as postulated by Grobstein. These molecules are variously essential for cell survival (avoidance of cell death by apoptosis), cell division (proliferation), differentiation (acquisition of specialized functions), and morphogenesis (acquisition of specialized form) during normal development. Transcription factors are proteins that bind to DNA and switch on or off the activity (i.e., RNA transcription) of diverse genes. Hence, they alter gene *expression* or activity and act as "conductors of the orchestra" of genes during development. Growth factors are produced by the embryonic urinary tract and can be considered as locally-acting hormones. Cell adhesion molecules act as "sticky" molecules that facilitate adhesion of cells to other cells and to adjacent matrices.

More recently, it has been realized that not all aspects of kidney differentiation can be explained by interaction of the bud and renal mesenchyme. It has been established, for example, that the renal capsule and interstitial/stromal cells have important "nurturing influences" with regard to nephron formation.[26] Furthermore, the molecular bases for supportive signaling between urothelial and smooth muscle precursors in the ureter and urinary bladder are being unraveled. Table 12-1 summarizes some of the genes that control urinary tract development based on analyses of mutant mice (i.e., animals genetically engineered to lack the activity of specific genes). Table 12-2 summarizes some of the general messages for human disease to be learned by studying mutant mice (for original citations, see Woolf and Jenkins[3]).

EFFECTS OF PERTURBED EMBRYONIC/FETAL MILIEU ON URINARY TRACT DEVELOPMENT AND EXPRESSION OF DEVELOPMENTAL GENES

Obstruction of Urine Flow

Posterior urethral valves occur in about half of all young boys with end-stage renal failure.[20] In humans at risk of congenital obstructive nephropathy, the idea of prenatal surgical intervention makes intuitive sense, and vesico-amniotic shunting and even fetal urethral valve ablation are feasible. Although there is some support from meta-analysis that perinatal survival is increased by fetal surgery, it is unclear whether long-term renal or bladder function is improved by prenatal versus postnatal surgery.[27] Prospective studies in which subjects are randomized to active fetal treatment and control fetal groups, have yet to be reported.

An interesting variation on the theme of prenatal urinary flow impairment is the acquisition of a "neurogenic bladder" before birth as a result of maternal varicella-zoster infection.[28] Sheep experiments that model urethral valves clearly demonstrate how bladder outflow impairment perturbs differentiation of the kidney and the bladder itself.[29-32] When obstruction is initiated early, renal histology often resembles Potter type IV malformation, with a nephrogenic zone replaced by cysts; fibrosis and hypoplasia typically follow obstruction initiated later in gestation. In fetal sheep, surgical decompression of obstructed urinary tracts appears to improve renal developmental potential.[33] Complete unilateral ureteric ligation in fetal sheep leads to acute (within days) changes in the forming kidney, with loss of precursor cells and formation of glomerular cysts in the periphery of the organ and distortion of the medullary collecting ducts. These morphologic changes are accompanied by altered expression of genes, including transforming growth factor β1, α-smooth muscle actins, and those genes coding for proteins affecting turnover of extracellular matrix.[34-36] The altered expression of similar genes has been demonstrated in human renal dysplastic tissues, and at least some probably directly perturb normal differentiation.[37] The topic has undergone several excellent reviews.[38,39]

Teratogens and Maternal Dietary Factors

Several agents have been anecdotally implicated as human renal tract teratogens, including angiotensin-converting enzyme inhibitors (ACEIs) and vitamin A (both discussed in this section), as well as ethanol, cocaine, glucose (i.e., hyperglycemia in maternal diabetes mellitus), nonsteroidal anti-inflammatory drugs, corticosteroids, and thalidomide.[40-43] Certainly, in animals, studies have proved that several such agents can perturb urinary tract development.[44] On the other hand, a history of exposure to specific teratogens appears to be rather unusual in humans with major renal tract malformations; whether all human reports of renal teratogenesis represent true examples of "cause and effect" is uncertain.

Table 12-1 Urinary Tract Malformations in Mice with Mutations of Defined Genes*

Gene Symbol	Gene Name	Associated Malformations
Genes Coding for Transcription Factors and Related Molecules		
Bf2	Brain factor 2/homologue of *Drosophila* forkhead	Renal hypoplasia
Brn1	Brain 1	Retarded loop of Henle development
Emx2	Empty spiracles 2	Renal agenesis
Foxc1	Forkhead box c1	Duplex kidney
Foxc2	Forkhead box c2	Renal hypoplasia
Foxd1	Forkhead box c2	Fused kidneys
Hnf1b	Hepatocyte nuclear factor 1β	Renal cysts, dysplasia
Hoxa11/Hoxd11 (†)	Homeobox a11 and d11	Renal agenesis or hypoplasia
Lim1	Lim homeobox 1	Absent kidneys
Lmx1b	Lim homeobox transcription factor 1β	Glomerular podocyte immaturity
N-Myc	Myelocytomatosis-related oncogene	Hypoplastic mesonephros
Pax2	Paired box 2	Renal agenesis in null mutant; renal hypoplasia in heterozygous mice
Pod1	Podocyte 1	Failure of renal epithelial differentiation
Rara/Rarb2 (†)	Retinoic acid receptor α and β2	Kidney and ureter malformations
Sall1	Sal-like 1/homologue of *Drosophila* spalt	Renal agenesis
Tshz3	Homologue of *Drosophila* teashirt	Congenital hydronephrosis and failure of smooth muscle differentiation
Six1	Homologue of *Drosophila* sine oculis	Renal agenesis
Wt1	Wilms' tumor 1	Renal agenesis in null mutants; proteinuria in heterozygous mice
Genes Implicated in Growth Factor Signaling		
Agt	Angiotensinogen	Hypoplastic papilla and hypotension
Agtr1a/Agtr1b (†)	Angiotensin receptor type 1a and 1b	Hypoplastic papilla
Agtr2	Angiotensin receptor type 2	Diverse urinary tract malformations
Angptl2	Angiopoietin 2	Disorganized peritubular capillaries
Bmp4	Bone morphogenetic protein 4	Diverse urinary tract malformations in heterozygous mice
Bmp7	Bone morphogenetic protein 4	Renal dysplasia
Efnb2	Ephrin b2	Persistent cloaca
Fgf7	Fibroblast growth factor 7	Renal hypoplasia
Gdnf	Glial cell line-derived neurotrophic factor	Renal agenesis
Gremlin	A Bmp antagonist	Renal agenesis
Notch2	Receptor for delta	Glomerular capillary defects when gene is underactive
Pdgfrb	Platelet-derived growth factor receptor B	Absent mesangial cells
Ret	Rearranged during transfection/Gdnf receptor	Renal agenesis or dysplasia
Robo2	Roundabout 2; receptor for slit 2	Duplex kidneys
Shh	Sonic hedgehog	Renal hypoplasia, ureter malformations, persistent cloaca
Slit2	Homologue of *Drosophila* slit	Duplex kidneys
Spry1	Homologue of *Drosophila* sprouty; modulates growth factor signaling	Duplex kidneys
Wnt4	Wingless-type MMTV integration site family member 4	Renal hypoplasia
Wnt11	Wingless-type MMTV integration site family member 11	Renal hypoplasia
Vegf	Vascular endothelial growth factor	Congenital glomerular disease

(Continued)

Table 12-1 Urinary Tract Malformations in Mice with Mutations of Defined Genes—cont'd

Gene Symbol	Gene Name	Associated Malformations
Genes Coding for Cell Adhesion/Extracellular Matrix Proteins		
Fras	Fraser syndrome 1	Renal agenesis
Frem2	Fras1-related extracellular matrix 1	Diverse renal malformations and cysts
Itga8	Integrin α8	Dysplastic kidneys
Lamab2	s-Laminin/laminin β2	Nephrotic syndrome
Nephrin	Congenital nephrotic syndrome 1; NPHS1	Congenital nephrotic syndrome
Genes Coding for Diverse Other Classes of Proteins		
Bcl2	B-cell CLL/lymphoma 2; cell survival molecule	Renal hypoplasia and apoptosis
Cox2	Cyclooxygenase 2; enzyme	Renal hypoplasia
Eya1	Eyes absent 1	Renal agenesis
Hs2st	Heparan sulphate 2-sulphotransferase	Renal agenesis
Mpv17	Peroxisomal membrane protein disrupted by viral insertion	Glomerulosclerosis
nNOS	Neuronal nitric oxide synthase	Hypertrophic dilated bladders
Pkd1	Polycystin 1	Metanephric cysts in null mutants; postnatal kidney cysts in heterozygous mice
Pkd2	Polycystin 2	Metanephric cysts in null mutants; postnatal kidney cysts in heterozygous mice
UpII	Uroplakin II	Hydronephrosis and vesicoureteric reflux
UpIII	Uroplakin III	Hydronephrosis and ureteric obstruction

*Unless otherwise stated, the malformations occur in "null mutants" with no gene activity; in other cases, the disease occurs in mice with one copy of the gene ablated (i.e., heterozygous mice). A dagger (†) indicates that the phenotype is present when two similar (homologous) genes are mutated.

Table 12-2 Lessons for Human Congenital Urinary Tract Disease To Be Learned from the Study of Mutant Mice

The same type of urinary tract malformation can result from mutation of quite different genes.

The severity of urinary tract malformation may be modulated by the "background" of the animal, because individuals from different strains may harbor minor genetic differences called "polymorphisms."

Sometimes, more than one closely related gene must be mutated before development is perturbed.

"Urinary tract development genes" are often also active in other organs, where they are also critical for development.

Some molecules that control mouse urinary tract development are also implicated in human disease.

Vitamin A (retinol), derived from the mother, is converted by the fetus to the bioactive molecule, all-*trans* retinoic acid. From genetic and dietary experiments downregulating this pathway, it is known that vitamin A is required for normal differentiation of the kidney and lower urinary tract, affecting gene expression and cell turnover.[4,45] However, high doses of retinoic acid are teratogenic, generating metanephroi that either undergo apoptotic regression or become cystic.[46] In this case, the expression of the Wt1 transcription factor is dramatically reduced in the nascent renal mesenchyme. In humans and animals, high doses of vitamin A are associated with renal agenesis, and sometimes with so-called caudal regression, the reduction of distal structures including the sacrum and hindlimbs.[47-49]

In view of the possible teratogenic effects of ACEIs (and angiotensin receptor–blocking drugs), the use of such agents should be avoided in hypertensive women who are pregnant.[50-52] Diverse renal disorders have been reported in offspring of mothers treated with ACEIs, including renal tubular dysgenesis, neonatal acute renal failure, and hypotension; skull malformations also occur. On the other hand, such complications are by no means inevitable after fetal exposure to such agents. For example, in a study of 19 such pregnancies, only 1 infant had anuria needing dialysis. Although some have attributed all the detrimental effects to hypotension and hemodynamic alterations, it is clear from animal experiments that angiotensin also directly mediates renal tract differentiation, especially by modulating apoptosis in early metanephrogenesis, and then morphogenesis of the renal papilla and ureteral smooth muscle at later stages.[53]

Data from animals show that maternal diet (e.g., the amount of protein ingested by the mother) programs the trajectory of growth of the embryonic kidney, altering cell turnover and gene expression at a time when nephrons and glomeruli have yet to form.[54,55] The human implication is that the amount of protein ingested from the time of conception through the first 5 or 6 weeks of gestation may affect kidney

Table 12-3 Selected Human Multiorgan Syndromes Associated with Urinary Tract Malformations

Syndrome	Genetic Basis	Associated Malformations
Apert's syndrome	*FGFR2* mutation (codes for a growth factor receptor)	Hydronephrosis and duplicated renal pelvis with premature fusion of cranial sutures and digital anomalies
Bardet-Biedl syndrome	Mutations of several genes implicated (some code for centrosomal proteins)	Renal dysplasia and calyceal malformations with retinopathy, digit anomalies, obesity, diabetes mellitus, and male hypogonadism
Beckwith-Wiedemann syndrome	*p57KIP2* mutation in a minority of patients (codes for a cell cycle protein)	Widespread somatic overgrowth with large kidneys, cysts, and dysplasia
Branchio-oto-renal syndrome	*EYA1*, *SIX1*, and *SIX5* mutations (code for transcription factor proteins)	Dominant mutations: hearing loss, preauricular pits, branchial clefts
Camptomelic dysplasia	*SOX9* mutation (codes for a transcription factor)	Diverse renal and skeletal malformations
Carnitine palmitoyltransferase II deficiency	Gene coding for this enzyme is mutated	Renal dysplasia
CHARGE association	*CHD7* mutation (codes for a DNA-binding protein)	Diverse urinary tract malformations can occur
Denys-Drash syndrome	*WT1* mutation (codes for a transcription factor)	Mesangial cell sclerosis and calyceal defects
DiGeorge syndrome	Microdeletion of 22q11 (probably several genes involved), including *TBX1* (codes for a transcription factor)	Congenital heart disease, hypocalcemia, immunodeficiency, and neurocognitive disorders
Fanconi anemia	Several mutant genes implicated (some code for proteins involved in DNA repair)	Renal agenesis, ectopic/horseshoe kidney, anemia, and limb malformations
Fraser syndrome	*FRAS1* and *FREM2* mutations (code for putative cell adhesion molecules)	Renal agenesis and dysplasia, digit and ocular malformations
Glutaric aciduria type II	Glutaryl–coenzyme A (CoA) dehydrogenase mutation	Cystic and dysplastic disease
HDR syndrome	*GATA3* mutation (codes for a transcription factor)	Renal agenesis, dysplasia, and vesicoureteric reflux occur
Kallmann's syndrome	*KAL1* mutation in X-linked form (codes for a cell adhesion molecule); *FGFR1* mutation in autosomal form (codes for a growth factor receptor)	Renal agenesis and dysplasia in X-linked form
Klinefelter's syndrome	47,XXY	Renal agenesis, small firm testes, gynecomastia, azoospermia, and hypergonadotropic hypogonadism
Meckel's syndrome	Several loci implicated (one contains a gene coding for a transmembrane protein of unknown function)	Cystic renal dysplasia, central nervous system and digital malformations
MURCS association	Genetic basis undefined	*Mü*llerian duct aplasia-hypoplasia, *r*enal malformations, and *c*ervicothoracic *s*omite dysplasia
Oral-facial-digital syndrome type I	*OFD1* mutation (codes for a centrosomal protein)	Glomerular cysts with facial and digital anomalies
Poland's syndrome	Genetic basis undefined	Renal agenesis, unilateral hypoplasia of pectoralis major muscle, and ipsilateral syndactyly
Renal-coloboma syndrome	*PAX2* mutation (codes for a transcription factor)	Renal hypoplasia, vesicoureteric reflux, and visual impairment
Renal cysts and diabetes (RCAD) syndrome	*HNF1B* mutations (codes for a transcription factor)	Renal dysplasia, cysts and hypoplasia, diabetes mellitus, hyperuricemia, and uterine malformations
Rokitansky-Kuster-Hauser syndrome	*WNT4* mutation (codes for a growth factor)	Renal agenesis, absent/rudimentary upper vagina and uterus
Simpson-Golabi-Behmel syndrome	*GPC3* mutation (codes for a proteoglycan)	Renal overgrowth, cysts, and dysplasia

(Continued)

Table 12-3 Selected Human Multiorgan Syndromes Associated with Urinary Tract Malformations—cont'd

Syndrome	Genetic Basis	Associated Malformations
Smith-Lemli-Opitz syndrome	*DHCR7* mutation (codes for a protein involved in cholesterol biosynthesis)	Renal cysts and dysplasia
Townes-Brocks syndrome	*SALL1* mutation (codes for a transcription factor)	Renal agenesis and other urinary tract malformations, imperforate anus, triphalangeal/bifid thumb, rocker-bottom feet, sensorineural hearing loss, hypospadias
Urofacial (Ochoa) syndrome	Locus on 10q (gene undefined)	Congenital obstructive bladder and kidney malformation with abnormal facial expression
Urogenital adysplasia syndrome	Some cases have *HNF1B* mutation	Renal dysplasia and uterine anomalies
VACTERL association	Genetic basis unknown apart from one report of mitochondrial gene mutation	Cardiac, tracheoesophageal, renal, radial, and other limb anomalies occur
WAGR syndrome	*WT1* and *PAX6* contiguous gene defect (code for transcription factors)	Wilms' tumor, aniridia, genital and renal malformations, mental retardation
Williams-Beuren syndrome	Microdeletion of 7q11.23	Renal agenesis, developmental delay, cardiovascular anomalies, mental retardation, and facial dysmorphology

CHARGE association = *c*oloboma, *h*eart malformation, choanal *a*tresia, *r*etardation, *g*enital and *e*ar anomalies; HDR syndrome = *h*ypoparathyroidism, sensorineural *d*eafness, and *r*enal anomalies; MURCS = *mü*llerian duct aplasia-hypoplasia, *r*enal malformations, and *c*ervicothoracic *s*omite dysplasia; VACTERL association = *v*ertebral defects, imperforate *a*nus, *t*racheo*e*sophageal fistula, and *r*adial and renal dysplasia, plus *c*ardiac abnormalities and nonradial *l*imb defects; WAGR syndrome = *W*ilms' tumor, *a*niridia, *g*enital and renal malformations, mental *r*etardation.

growth. Perhaps variations in maternal diet partly explain not only the wide range of nephron numbers per kidney found in "normal" humans but also the differences in nephron number between normotensive individuals and those with essential hypertension.[8] Although an increased risk of elevated microalbuminuria was reported in adults who were conceived and born during times of famine, it is unclear whether modest dietary alterations program human development of the urinary tract.[56]

HUMAN MALFORMATION SYNDROMES INVOLVING THE URINARY TRACT

In some cases, kidney and lower urinary tract congenital anomalies occur in association with a multiorgan malformation syndrome that commonly affects the central nervous, cardiovascular, or skeletal systems. Although each malformation syndrome is rare, there are very many varieties of such syndromes, and collectively they account for considerable morbidity. Some are associated with gross chromosomal anomalies such as trisomies, 4p-syndrome, and dup(10p)/del(10q),[57-60] but gross cytogenetic aberrations are absent in most cases of urinary tract malformation syndromes. Other renal malformation syndromes are inherited in mendelian patterns, and in several of them disease loci and mutations have been defined (Table 12-3). Further information can be found on the Online Mendelian Inheritance in Man Web site (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim [accessed January 2009]).

In the remainder of this review, four malformation syndromes are described as examples in which advances in genetics illuminate the pathogenesis of abnormal urinary tract development. The question of whether nonsyndromic human urinary tract anomalies may have genetic bases is then considered.

The Renal-Coloboma Syndrome

As human renal mesenchymal cells differentiate into nephrons, they aggregate and undergo a burst of proliferation with increased expression of the PAX2 transcription factor; concurrently, proliferative termini of adjacent ureteric bud branches express PAX2.[61] Urinary tract growth is impaired in mice with inactivating mutations of this gene.[62,63] Null mutants (i.e., mice with both alleles mutated) lack kidneys and ureters because the ureteric bud fails to branch from the mesonephric duct. Haploinsufficiency (i.e., a partial lack of functional protein) in heterozygous mice is associated with renal hypoplasia and, in some cases, hydronephrosis and hydroureter.

The human renal-coloboma syndrome has a striking similarity to the syndrome in mice with one inactivated allele;, it comprises blindness (or lesser degrees of visual impairment) due to an optic nerve malformation called a coloboma, together with vesicoureteric reflux and hypoplastic kidneys. Sanyanusin and colleagues[64] first described heterozygous mutations of *PAX*, and several other reports followed in the next decade.[65-67] The eye disease in affected humans (and mice) is explained by the fact that expression of the same gene is needed during ocular development. PAX2 is expressed in human Wilms' tumors and in human renal carcinoma.[68,69] Indeed, PAX2 transforms murine cells and inhibits the promoter of TP53, a tumor suppresser.[70]

Recent experiments have shown that PAX2 enhances urinary tract growth by preventing the untimely apoptotic death of embryonic precursor cells[71] and also by stimulating the expression of a growth factor called WNT4.[72] Of note, mutation of the gene coding for this growth factor has been reported[73] in a patient with the Rokitansky-Kuster-Hauser syndrome (malformations of the renal tract and müllerian duct derivatives).

Finally, PAX2 is highly expressed in human dysplastic kidney cysts, which contain highly proliferative cells.[61] The cause of this prominent expression is not known, but PAX2 may be one factor that accounts for perturbed epithelial growth in, for example, multicystic dysplastic kidneys.

Kallmann's Syndrome

X-linked Kallmann's syndrome is caused by mutations of *KAL*, a gene on the short arm of the X chromosome.[74,75] Anosmia and hypogonadotropic hypogonadism occur in affected males because of defective prenatal migration of olfactory and gonadotrophin-releasing hormone neurons from the nasal placode into the forebrain; moreover, the olfactory bulb fails to grow and is hypoplastic.[76] The syndrome affects 2% of hypogonadal males.[77] This syndrome is a human genetic model of renal agenesis; the absent kidney is usually unilateral, resulting in a solitary functioning kidney.[78,79] Patients with urinary tract agenesis also lack the vas deferens, itself derived from the mesonephric duct, which also gives rise to ureteric bud derivates. The *KAL* gene is expressed in the developing central nervous and urinary tract[80] and the encoded protein, called anosmin 1, immunolocalizes to basement membranes of the mesonephric duct and its collecting duct branch derivatives.[81] Antibodies to anosmin 1 block the formation of the collateral branches of rat olfactory bulb output neurons,[82] and there is evidence that anosmin 1 modulates growth factor signaling in neuroblasts.[83] Collectively, the data are consistent with a role for KAL1/anosmin 1 in mediating cell adhesion during ureteric bud growth, although the exact mechanisms remain unknown.

Renal Cysts and Diabetes Syndrome

The renal cysts and diabetes (RCAD) syndrome is caused by mutations of the transcription factor gene, *hepatocyte nuclear factor* 1β (*HNF1B*). The key features are diabetes mellitus and also renal malformations of diverse phenotypes, including cystic, dysplastic, and hypoplastic kidneys (organs having fewer nephrons than normal), as well as a solitary functioning kidney, all in the absence of lower urinary tract obstruction.[67,84-86] The diagnosis should be suspected in an individual who has a urinary tract anomaly and glucose intolerance, especially if a first-degree relative has either disorder; another clue, in women, is the occurrence of uterine malformations. Human *HNF1B* heterozygous mutations can occur de novo, or they can be inherited in a dominant manner. *HNF1B* gene activity can be detected in several embryonic human organs in which mesenchymal/epithelial interactions occur (e.g., stomach, lung, pancreas, kidney), with prominent expression in the stalks of fetal kidney collecting ducts but not in the branching, proliferating tips of ureteric bud branches.[86] This suggests that HNF1B may serve as a "maturation factor." Data from mutant mice have shown that the gene is indeed important for maintaining the differentiated state of renal epithelia and that a deficiency of gene activity leads to excess proliferation and cystic changes in kidney tubules.[87]

GENETICS OF NONSYNDROMIC HUMAN URINARY TRACT MALFORMATIONS

Is there any evidence that mutations have a role in the nonsyndromic urinary tract anomalies more commonly encountered by urologists and nephrologists? It is common clinical experience that most cases of renal agenesis and dysplasia appear to be sporadic. However, in 1974, Cain and colleagues[88] cited 12 reports of familial renal malformations and described a kindred with two siblings: the first with bilateral renal agenesis and the second with unilateral agenesis and contralateral dysplasia. Others reported that first-degree relatives of patients with bilateral urinary tract agenesis had a 10-fold higher incidence of solitary kidney compared with controls.[89] In fact, there is considerable anecdotal evidence establishing the possibility of a genetic basis of diverse other nonsyndromic urinary tract malformations. These include kindreds with renal agenesis,[90-93] renal dysplasia,[93-95] multicystic dysplastic kidney,[96,97] renal hypoplasia,[95,98,99] pelviureteral junction obstruction,[100] vesicoureteric reflux,[101,102] and posterior urethral valves.[103,104]

Angiotensin II Pathway Mutations and Urinary Tract Malformations

Considerable evidence from animal experiments suggests that angiotensin is important for urinary tract development. Mice engineered to lack both angiotensin II type 1A and 1B receptor genes or the angiotensinogen gene fail to develop a normal renal medulla and have delayed glomerular maturation.[105] Similar effects can be elicited by pharmacologic inhibition of angiotensin II activity in rodents during early postnatal life.[53] As discussed earlier, drugs that block angiotonin II signaling are associated with urinary tract teratogenesis; some affected individuals also have a skull malformation called hypocalvaria.[106] A strikingly similar malformation spectrum also can occur in the absence of teratogen exposure.[12] Gribouval and associates[107] postulated that such individuals harbor mutations that affect angiotensin signaling and indeed found homozygous or compound heterozygous mutations in the genes encoding renin, angiotensinogen, angiotensin-converting enzyme, or angiotensin II receptor type 1.

Null mutations of the *angiotensin II type 2 receptor* gene (*AGTR2*, formerly designated *AT2*), which is located on the X chromosome, lead to a spectrum of urinary tract malformations in male mice, including renal dysplasia, hypoplasia, hydronephrosis, and vesicoureteric reflux.[108] The basis for this phenotype is thought to be delayed apoptosis of mesenchymal cells throughout the urinary tract.[108] Nishimura and coworkers[108] reported the association of a polymorphism of intron 1 of the human *AGTR2* gene (the A1332G transition, which perturbed messenger RNA splicing) in patients with multicystic dysplastic kidneys and/or pelviureteral obstruction; the polymorphism occurred in 19% to 42% of normal subjects and in 74% to 77% of patients. Subsequently, Hohenfellner and associates[109] reported an association of this polymorphism with obstructive megaureter. It also has been observed that different types of urinary tract malformation can occur in the same kindred.[95,110-112] This is compatible with the hypothesis that specific mutations can potentially affect the development of the whole urinary tract but that the final phenotype depends on modifying factors, either genetic or environmental, which vary from individual to individual. Perhaps *AGTR2* polymorphisms are one such modifying factor.

Genetics of Primary, Nonsyndromic Vesicoureteric Reflux

The term *vesicoureteric reflux* (VUR) describes the passage of urine from the bladder into the upper urinary tract. It can occur secondary to bladder outlet obstruction or as part of a multiorgan syndrome such as that associated with *PAX2* mutation. Much more commonly, it is primary and nonsyndromic, and screening with cystograms suggests that the disorder affects between 1% and 10% of children.[113] Although there is no experimental evidence indicating that reflux in the absence of obstruction is harmful to the kidney,[114] associated renal parenchymal disease, or "reflux nephropathy," causes 5% to 15% of the cases of chronic renal failure in children and adults.[20,113] The nephropathy is likely to have two main etiologies. First, the passage of infected urine into the renal parenchyma via compound papillae can lead to acute pyelonephritis followed by scarring; this is especially common in girls. Second, primary VUR can be associated with renal dysplasia and hypoplasia[16,115]; these patients are usually boys with severe grades of reflux. Genetics may play a role in the pathogenesis of primary VUR, because there is a markedly increased risk in immediate relatives of probands compared with the general population.[116,117] The inheritance in many kindreds appears to be dominant with variable penetrance and expression.[118] Feather and colleagues[101] reported the results of the first genome-wide search of VUR in seven European families with up to seven affected members who had an apparent dominant inheritance pattern. Although the data suggested the possibility of a locus on chromosome 1p, specific mutations remain to be defined, and two of the kindreds were not linked to this locus. More recently, a similar analysis using different families failed to confirm the 1p locus.[102]

Collectively, the observations are compatible with the hypotheses that mutations in different genes may give rise to the same type of urinary tract malformation (phenocopies), or that the interaction of more than one mutation may be required to generate disease, or both. Future studies may need to analyze many hundreds of smaller pedigrees to unravel the genetics of primary VUR, a strategy being followed by the United Kingdom Vesicoureteric Reflux DNA Collection (available at http://www.vur.org.uk/ [accessed January 2009]). Complementary clues in the search for "reflux genes" may also come from the analysis of rare individuals with congenital reflux who have small chromosomal deletions.[119] Recently, based on the observations that mice with mutations of genes coding for uroplakin (proteins that coat the luminal surface of the urothelium) are born with VUR and other ureter anomalies,[120-122] Jenkins and colleagues[123,124] sequenced human uroplakin genes in a series of children with bilateral renal dysplasia and kidney failure. Four de novo sequence changes were found in *UPK3A* and one inherited insertion in *UPK2*, and three of these individuals had severe VUR. In addition, Schonfelder and coworkers[125] reported another de novo *UPK3A* mutation in an individual with multicystic dysplastic kidney. Although these human observations are of interest, especially because some of the *UPK3A* mutations are predicted to have effects on uroplakin 3A functions,[126,127] uroplakin mutations will probably be implicated only in a small subset of individuals with primary VUR, perhaps being found more commonly in those with associated renal dysplasia.

Miscellaneous Anomalies of the Lower Urinary Tract

As reviewed by Weber and colleagues,[104] the medical literature contains rare reports of two male siblings being affected by posterior urethral valves. The most likely genetic hypothesis here is that this condition is a recessive disorder in which the full-blown disease is expressed only in males. By performing a genome-wide search in an extraordinary family with several surviving siblings affected by posterior urethral valves and prune-belly syndrome, Weber and associates[104] provided preliminary data for candidate loci on chromosomes 1q and 11p. Jenkins and colleagues[128] sequenced several candidate genes, including *UPK3A*, *HNF1B*, *SHH* (sonic hedgehog homologue), and *EFNB2* (ephrin B2), in 20 individuals with persistent cloaca, but, apart from one with a *UPK3A* mutation, no other genetic changes were identified.

The urofacial (Ochoa) syndrome, a disorder characterized by lower urinary tract and bowel dysfunction with an abnormal facial expression, has been mapped to chromosome 10q.[129] Nocturnal enuresis can occur in families, sometimes in an autosomal dominant pattern, and loci have been identified on chromosomes 8q, 12q, 13q, and 22q.[130] The genes implicated in urofacial syndrome and nocturnal enuresis remain undefined, but perhaps they are more likely to code for molecules that affect bladder function rather than proteins that cause primary alterations in urinary tract morphogenesis.

CONCLUSION

Malformations of the urinary tract are common causes of chronic renal failure in young children, and it is evident that mutations alter gene expression during development to cause some of these disorders. The most convincing studies come from the multiorgan malformation syndromes for which specific mutations have been defined. However, these syndromes are relatively rare, and most urinary tract malformations appear to occur in isolation. In some of these conditions, however, a genetic pathogenesis is strongly suggested by a positive family history and genetic linkage studies. One common example is primary VUR. Furthermore, sporadic malformations have been shown to be associated with polymorphisms of genes expressed during construction of the urinary tract. In the long term, an understanding of the genetic aspects of human urinary tract malformations will help to unravel the pathogenesis of these disorders and may facilitate the design of genetic screening tests with a view to early diagnosis and appropriate genetic counseling.

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For complete list of references log onto www.expertconsult.com

CHAPTER 13

PEDIATRIC URINARY TRACT INFECTIONS

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In infants and children, the urinary tract is a relatively common site of infection. Urinary tract infections (UTIs) result in significant acute morbidity as well as long-term medical problems including delayed hypertension and progressive renal dysfunction. Accurate diagnosis and timely treatment are vital in limiting these long-term sequelae, because the pediatric kidney is particularly susceptible to scarring and permanent renal damage. During the 1990s, bacterial and host characteristics were identified that may increase risk of renal parenchymal and functional loss. This chapter focuses on the pathogenesis and natural history of pediatric UTIs and discusses means of preventing renal damage.

INCIDENCE AND EPIDEMIOLOGY

Pediatric UTIs constitute a significant health care burden that has been poorly quantified. In the United States, infections of the urinary tract affect 2.4% to 2.8% of children every year and account for 1.1 million office visits annually. The cost of hospitalization alone for children with UTI totals more than $180 million per year without accounting for the ambulatory visits that account for the majority of UTI treatments.[1]

The incidence of UTI in the pediatric population varies based on age and gender. Only during the first year of life do males have a higher incidence of UTI when compared to females (0.7% versus 2.7%, respectively).[2] Furthermore, during the first 6 months of life, uncircumcised males have a 10- to 12-fold increased risk compared to circumcised males for development of UTI.[3] Until the age of 5 years, the incidence of UTI is 0.9% to 1.4% for girls and 0.1% to 0.2% for boys.[4] With advancing age, the incidence decreases to less than 1% in school-age boys but rises to 1% to 3% in school-age girls.[5-7] The variation in incidence among boys and girls demonstrates the importance of specific host characteristics that alter the risk of bacteriuria.

CLASSIFICATION

Previously, UTIs were classified in numerous descriptive ways, such as complicated versus uncomplicated, or upper versus lower tract. For practical purposes, pediatric UTIs may simply be categorized into two types: first infections and recurrent infections. The recurrent infections may then be categorized as (1) unresolved bacteriuria during therapy, (2) bacterial persistence at an anatomic site, and (3) re-infections. This simplified approach underscores the importance of the first occurrence of a UTI and the management and treatment implications surrounding these infections.

In infants and children, urinary infections are often associated with underlying anatomic abnormalities that predispose and complicate bacteriuria. First infections should therefore be considered complicated and should undergo an imaging evaluation. Typically, correctable causes of bacterial persistence are discovered early, on this initial radiologic evaluation (Table 13-1).

Most recurrent UTIs are re-infections with the same or a different pathogen; the infecting organisms ascend from the bowel and have no surgically correctable source. Occasionally, bacteriuria is unresolved because of inadequate therapy related to bacterial resistance to the selected therapeutic agent, inadequate antimicrobial urinary concentration due to poor renal concentration or poor gastrointestinal malabsorption, or an infection involving multiple organisms with differing antimicrobial susceptibilities. Unresolved infections can usually be treated successfully once proper culture and antimicrobial sensitivity patterns are obtained. However, knowledge of bacterial biofilm formation emphasizes that antimicrobial treatment may be more complex than antimicrobial sensitivity patterns alone would indicate. Bacterial persistence occurs when a nidus of infection is not eradicated after the initial antibiotic course. The discovery of surgically correctable sources of bacterial persistence is obviously important.

PATHOGENESIS

Bacterial genetic clonal studies confirm that entry into the urinary tract occurs through the suspected fecal-perineal-urethral route, with subsequent retrograde ascent of periurethral bacteria.[8] Once bacteria have gained entry into the urinary system, they must overcome host defenses including urethral washout, epithelial shedding, periurethral glandular secretion, and Tamm-Horsfall glycoprotein before they can adhere to the bladder mucosa. These factors vary by gender, age, and individual host characteristics, resulting in variable likelihood for bacterial ascent.[9]

Other routes of infection include hematogenous, lymphatic, and direct extension from adjacent organs. Infection of the urinary tract via hematogenous spread is uncommon and usually occurs in children who are immunocompromised. Organisms that may spread hematogenously to the urinary tract include *Staphylococcus aureus*, *Candida* species, and tuberculosis. Infection of the urinary tract by means of lymphatic channels is rare. It is hypothesized that bacteria may travel through rectal, colonic, or periuterine lymphatics to infect the urinary tract. Genitourinary tract fistulas, such as vesicovaginal fistulas and vesicointestinal fistulas, can result in urinary infections by direct extension.

Bacteria

The enteric gram-negative Enterobacteriaceae, most frequently *Escherichia coli*, are the bacteria most commonly infecting the urinary tract.[10-12] Specific *E. coli* serotypes (e.g., O1, O2, O4, O6, O7, and O75), identified by their cell wall O-antigens, are associated with pediatric UTIs.[11,12] With increased treatment of gram-negative infections with broad-spectrum antibiotics, the gram-positive *Enterococcus faecalis* is a more commonly found uropathogen.[13]

Bacterial cell surface structures called *pili* or *fimbriae* may increase virulence potential by mediating bacterial adherence to uroepithelial cells. These pili are classified on the basis of their ability to agglutinate red blood cells (hemagglutination) of different animal species as well as the ability of various sugars to block this hemagglutination reaction.[14,15] Using

Table 13-1 Correctable Causes of Bacterial Persistence in Children

Infection stones
Infected nonfunctioning or poorly functioning kidneys or renal segments
Infected ureteral stumps after nephrectomy
Vesicointestinal or urethrorectal fistula
Vesicovaginal fistula
Infected necrotic papillae in papillary necrosis
Unilateral medullary sponge kidney
Infected urachal cyst
Infected urethral diverticulum or periurethral gland

these characteristics, Kallenius and associates discovered that pyelonephritogenic *E. coli* cause mannose-resistant hemagglutination (MRHA) of human red blood cells.[16] Characterization of this reaction demonstrated that the terminal glycolipid of the human red cell P blood group antigen is a receptor that binds P-fimbriae on these *E. coli* cells.[17-19] Receptors for P-fimbriae are also present on uroepithelial cells, as well as renal tubular cells in the kidney, and in a similar fashion mediate the binding of bacteria to these cells. MRHA characteristics and P blood group–specific adhesins (P-fimbriae or P-pili) are two important markers for *E. coli* virulence.[17,19]

The importance of these two virulence characteristics has been supported by studies examining their association with clinically diagnosed pyelonephritis and cystitis. Vaisanen and colleagues demonstrated that both MRHA and P-fimbriae are present on most *E. coli* strains causing clinically diagnosed pyelonephritis in children: 29 (91%) of 32 strains were positive for MRHA, and 81% of those were also positive for P-fimbriae.[19] Similarly, in a study of 35 children with pyelonephritis, Kallenius and associates found P-fimbriae on 94% of *E. coli* causing acute pyelonephritis. In contrast, only 19% (5/26) of children with clinically diagnosed cystitis, 14% (5/36) of *E. coli* causing asymptomatic bacteriuria, and 7% (6/ 82) of *E. coli* from the feces of healthy children had P-fimbriae expression.[16]

More recently, however, when dimercaptosuccinic acid (DMSA) renal scanning has been used to differentiate pyelonephritis from cystitis, the relationship between P-fimbriated strains of *E. coli* and susceptibility to pyelonephritis has been less clear. There is evidence to suggest that P-fimbriated *E. coli* are simply more likely to induce a febrile reaction in the host, irrespective of kidney involvement.[20,21] A possible mechanism or mediating factor is the demonstration of higher urinary interleukin-6 response in children infected with P-fimbriated *E. coli* than in those infected by other strains.[22] It has been suggested, moreover, those UTIs caused by P-fimbriated strains[23] and those generating bacterial biofilms may need longer antimicrobial courses than those caused by other strains.

Animal models have revealed a potential new paradigm for acute and recurrent UTI. Attachment between the uroepithelial cell and the bacterial cell via factors such as type 1, P-pili, and fimbriae is known to be the initiating event. This attachment has now been discovered to trigger a series of molecular interactions in which the adhesion-receptor complexes cause uptake of the bacteria into the bladder surface umbrella cell.[24] In a defensive response, the uroepithelial cells are rapidly shed.[25] The bacteria are able to enter the epithelial cells, interacting with lipid rafts and uroplakins to form intracellular bacterial communities. These bacterial communities develop and transform into an organized biofilm with a more coccoid form. As these communities enlarge, they form cellular "pods" that protrude from the surface and may detach and disseminate.[26] This biofilm may allow microbial adaptation to variable environments and subsequent aggregate detachment that may cause systemic infection, antimicrobial resistance via plasmid exchange, endotoxin production, and overall increased resistance to host immune systems.[27]

Host Susceptibility Factors

Although bacterial virulence characteristics may increase the likelihood that any periurethral bacterial strain will enter the urinary tract, there are also host-specific characteristics that alter risk of bacteriuria and subsequent renal damage.

Age

Males and females have a higher incidence of bacteriuria before 1 year of age than at any other time during childhood. This age-dependent relationship may be related to several other host factors, including periurethral colonization, breast feeding, and immature immune status.

Gender

As discussed earlier, males younger than 1 year of age are more inclined to develop UTI than similarly aged females, and girls are more susceptible thereafter. Although many factors, including urethral length, prostate, and foreskin, have been hypothesized to account for this difference, the reasons are not entirely known.

Periurethral Colonization

Times and conditions of increased periurethral colonization are associated with increased risk of UTI. During the first few months after birth, the periurethral area of healthy girls and boys is heavily colonized with aerobic bacteria (especially *E. coli*, enterococci, and staphylococci).[28] Epidemiologic data have shown that the incidence of UTI is much higher during this time than at any subsequent time in the next few years. This colonization decreases after 6 months, and it is unusual in children who are without recurrent infections after age 5 years. Thereafter, only those women and children who suffer repeated UTIs remain colonized by periurethral gram-negative bacteria.[28-30]

Preputial Skin

The association of the foreskin and neonatal UTI has caused controversy regarding the advantages and disadvantages of circumcision.[31] This controversy has resulted in numerous editorials and recommendations by the American Academy of Pediatrics.[32-40]

During the first few months of life, there appears to be an association between the presence of foreskin, periurethral and preputial colonization, and UTI. Wiswell and associates found that, during the first 6 months of life, periurethral uropathogenic bacteria were cultured more frequently (using intraurethral and glanular cultures) from uncircumcised boys than from circumcised boys.[41] Uncircumcised male infants, moreover, have an increased relative risk of UTI (3.12) when compared to circumcised boys, but this risk decreases to 3.7 at 1 year and 3.0 at 3 years.[42] Several factors, including early immune status, unusual nosocomial colonization, breast feeding,[37] and other bacterial adherence factors,[43] are thought to result in the observed high colonization of the foreskin.

In a series of retrospective reviews of 55 worldwide U.S. Army Hospitals, Wiswell and Roscelli[44] examined the incidence of UTI diagnosed by catheterization or suprapubic aspirate in male infants hospitalized from 1974 to 1983. They found that the incidence of infection in uncircumcised males (468 of 41,799, or 1.12%) was greater than in circumcised males (193 of 175,317, or 0.11%). Female infants demonstrated an incidence of 0.57% (1164/205,212). The authors noted that most infections occurred during the first 3 months of life. Interestingly, they observed a significant decrease in the frequency of circumcision during the 10-year study period (from 85.4% to 73.9%). As the frequency of circumcisions decreased toward the end of the study, there was a concomitant increase in the total number of UTIs observed.[44,45] Wiswell subsequently concluded that UTIs were more frequent in uncircumcised boys.

More recently, a meta-analysis reviewing the published data concerning the effect of circumcision on the risk of UTI evaluated data on 402,908 children from 12 different studies. Circumcision was clearly associated with a significantly decreased risk of UTI (odds ratio, 0.13). These authors further concluded that, when the risks of UTI in normal boys and high-risk boys (i.e., those with recurrent UTI or high-grade vesicoureteral reflux [VUR]) are compared with the risks of circumcision, only boys at high-risk of UTI are likely to experience net clinical benefit.[46] Others have examined the rate of UTI in young boys before and after vesicoureteral reimplantation in which circumcision was or was not performed at the time of correction of reflux; no difference was found between any of the groups.[47] Although there may be difficulties with these studies related to retrospective analysis and selection bias, periurethral colonization has been associated with an increased risk of UTI in girls and women as well as male subjects.

At this time, there is no way of predicting whether a male infant with a normal urinary tract who gets a UTI has a genetic or familial predisposition for infection. Because few infant boys who suffer a neonatal UTI have a risk of a recurrent UTI after 1 year if they remain clear in the interim, the administration of prophylactic antibiotics for 6 months may be helpful. There is some evidence that, among premature boys who are hospitalized in neonatal intensive care units, circumcision may decrease the risk of recurrent UTI during this period.[48] There is currently no definitive evidence that prophylactic circumcision after a neonatal UTI prevents future infections in a boy older than 6 months.

Uroepithelial Adherence and Familial Factors

The existence of inherited risk factors for UTI is supported by clinical studies and suggests a genetic predisposition for recurrent UTI. Sisters of girls with recurrent UTIs have a higher incidence of significant bacteriuria on screening cultures than that expected for the normal population.[49] A possible mode of inherited risk was revealed when the P blood group antigen was recognized as a receptor for bacterial P-fimbriae. Because hosts with these receptors (i.e., the P blood group phenotype) might have special susceptibility to infection, children with recurrent infections were examined for the P blood group phenotype.[50] Whereas the P1 blood group phenotype was found in the 95% (35/36) of girls who had recurrent pyelonephritis with minimal (grade I) or no reflux, it was found in only 75% (63/84) of girls without infection. When girls with grade II to V reflux and pyelonephritis were examined, 27/32 (84%) were found to have the P1 blood group phenotype, an incidence similar to that found in individuals without infection.

These data suggest that host VUR contributes more to the infiltration of bacteria into the kidney than does bacterial virulence. However, among children with minimal or no reflux, P-fimbriae may be a major contributing factor. Other blood groups on the uroepithelial surface antigens (i.e., ABO, Lewis, and secretor phenotype), as well as the interleukin-8 (IL8) receptor (CXCR1) and the toll-like receptors, also appear to influence an individual's susceptibility to UTI.[51-54]

Native Immunity

The influence of the host's native cellular and humoral immunity on risk of UTI is unclear. UTIs are more commonly seen in infants during a time when their immune system is incompletely developed. Serum immunoglobulin G (IgG) as well as IgA are lowest during the first few months after birth, at a time when periurethral colonization is high in normal children.[55] Moreover, secretory IgA, an important human immunoglobulin at the secretory and mucosal surfaces of the body, is either absent or almost absent in the nasopharynx, gut, and urothelium during this time.[56-58]

The role played by urinary IgA in infants and children with UTI has not been examined extensively. Studies have demonstrated that children with recurrent UTI have lower urinary secretory IgA concentrations than children without infections.[56] Urinary IgA levels in infants and children during acute pyelonephritis were elevated compared with children without UTIs. These levels, however, are far below those found in adults.

The benefits of breast milk in preventing infection in infancy have been expounded for some time, but whether these benefits are related to colostral IgA or other factors is not known.[59] Case-control studies suggest that breast feeding may confer a protective effect against UTI during the first 7 months of life. These studies revealed that ongoing exclusive breast feeding produced a significantly lower risk of infection, and a longer duration of breast feeding resulted in a lower risk of infection after weaning, indicating a long-term mechanism. The protective role of breast feeding was strongest at birth and decreased after 7 months of age.[60] Further studies showed duration of breast feeding to be shorter in children who had UTI (9 versus 16 weeks in children who had exclusive breast feeding)[61] but concluded that full or partial breast feeding may confer a protective effect against UTI for the first 6 months of life.[62,63] Although the protective mechanism is unknown, the oligosaccharide content of the mother's breast milk and urine are the same as that of the breast-fed infant's urine, and these oligosaccharides may inhibit adherence of pathologic *E. coli* to the uroepithelium.[64] In addition, urinary secretory IgA levels were found to be higher in breast-fed compared with formula-fed infants.[65]

As expected, children with specific immune deficiency syndromes have altered immunity and often have increased risk of bacteriuria and progression of infection. About 20% of children infected with the human immunodeficiency virus get bacterial UTIs with both common and opportunistic organisms.[66]

Fecal Colonization

The composition of human fecal bacterial flora depends on the surrounding microbial ecology, native immunity, and microbe-altering drugs and foods. The importance of abnormal fecal colonization in neonates is emphasized by studies showing that fecal colonization with specific pyelonephritic bacteria may occur in a neonatal nursery or hospital, with subsequent bacteriuria or pyelonephritis developing several months later.[67]

The development of multiple antibiotic-resistant organisms in the gut through the use of antibiotic agents is well recognized. Because the fecal flora is commonly responsible for perineal and periurethral colonization, the importance of responsible antibiotic use cannot be overestimated. In one study, antibiotic treatment of schoolgirls with phenoxymethylpenicillin for recurrent infections, usually otitis media, caused recolonization and bacteriuria with strains more likely to be symptomatic.[68]

Genitourinary Anatomic Abnormalities

Genitourinary abnormalities may predispose as well as complicate bacteriuria secondary to inadequate clearance of uropathogens. Historically, UTI has been a marker for genitourinary tract abnormalities in children. However, with the widespread use of prenatal ultrasonography, these anatomic abnormalities are often identified before they become clinically evident. This suggests that, in areas with a high frequency of testing with prenatal ultrasonography, UTI in an infant may be associated with a varying incidence of genitourinary abnormalities.[69]

Conditions of genitourinary partial obstruction or renal functional impairment may create increased risk of renal damage due to poor or inadequate treatment. Nonfunctioning segments may also serve as nidus of bacterial infection and cause bacterial persistence because of difficulty in achieving adequate urinary antimicrobial concentrations. Several special conditions that may alter a child's risk for UTI are discussed in the following sections.

Vesicoureteral Reflux

VUR is common in children with UTI. Epidemiologic surveys have shown that between 21% and 57% of children who have had bacteriuria are subsequently found to have VUR.[11,70-72] However, no correlation between reflux and UTI predisposition has been found. The importance of reflux lies in the fact that it allows bladder bacteria renal access with subsequent potential for renal damage.

Persistent Vesicoureteral Reflux in Peripubertal Girls

Controversy exists as to whether girls approaching puberty who have persistent VUR risk increased renal damage. Although the prevalence of bacteriuria in pregnant and nonpregnant women is almost the same,[73] the incidence of pyelonephritis in pregnancy is greatly increased. If bacteriuria is left untreated, pyelonephritis develops in up to 30% of pregnant women[74] but rarely in nonpregnant women. This increased risk may be related to the hydronephrosis of pregnancy, which results from hormonal and mechanical changes. Increased compliance of the bladder and collecting system, bladder enlargement, and an enlarging uterus may cause some anatomic displacement of the bladder and ureters.[75] There are no data to suggest that pregnancy causes VUR, although women with reflux were at higher risk for developing pyelonephritis.[76]

Several studies suggest that postpubertal females who have VUR and a predisposition for frequent UTIs will continue to have this predisposition into adulthood and pregnancy.[7,70,72] Although reflux correction may decrease the likelihood of ascending pyelonephritis under normal circumstances, the nonrefluxing orifice may not offer the expected protection from pyelonephritis should bacteriuria occur during pregnancy. Therefore, both persistent reflux and the girl's predisposition for bacteriuria should be assessed before reflux correction is considered. Moreover, even with correction, patients should know that pyelonephritis during pregnancy is still possible, and routine bacteriuria screening should be performed.

Neurogenic Bladder

Children with neurogenic bladders and abnormally elevated bladder pressures risk increased renal damage from UTI for two reasons: elevated urinary tract pressures and increased frequency of instrumentation with subsequent infection. The combination of increased pressure from within the neurogenic urinary tract and the physiologic effects of UTI substantially increases the likelihood of renal parenchymal damage.[77] Specifically, a neurogenic bladder with chronically elevated bladder pressures may realize secondary VUR via decompensation of the ureterovesical junction.[78] Alternatively, elevated bladder pressures associated with a neurogenic bladder may cause obstruction with risk of renal damage.[79]

With a higher incidence of bacteriuria, a child with a neurogenic bladder may be at higher risk for febrile infections and possible renal damage. Clean intermittent catheterization (CIC) programs are useful for emptying the neurogenic bladder, but these catheterizations introduce bacteria. Although conclusions from previous studies involving CIC in children are limited, they all emphasize that bacteriuria and even pyuria occur commonly[80-83] but are usually asymptomatic.[81,82,84] Although complications of urinary calculi and epididymitis have been noted,[85] the long-term complications of children on CIC programs must be better defined. One investigation showed that the costly use of sterile catheters in CIC programs does not reduce the incidence of bacteriuria and therefore appears to have no proven benefit.[86]

Whereas prophylactic antibiotics may decrease, but not eliminate, bacteriuria in the short term,[81] their actual benefit is unproven. A study of 15 children receiving nitrofurantoin prophylaxis demonstrated a small decrease in bacteriuria (74% placebo versus 65% treated); however, the organism responsible for bacteriuria shifted to resistant organisms such as *Klebsiella* and *Pseudomonas*.[87]

NATURAL HISTORY

The natural history of the pediatric UTI is unpredictable and incompletely understood. Although it has been recognized that the pathogenesis of UTI in children differs from that in adults, UTI in children has often been studied without regard for age and other pediatric-specific factors. Research has shown, however, that about 3% of girls and 1% of boys develop a prepubertal UTI[12] and, of these children, 17% or more develop infection-related renal scarring. Among those with scarring, 10% to 20% become hypertensive, and a rare child develops progressive renal dysfunction culminating in end-stage renal disease (ESRD) (Fig. 13-1).

Cystitis and Pyelonephritis

Although a child's risk factors and the bacterial virulence may partially predict the course of a UTI, these factors alone are unhelpful in predicting who will develop pyelonephritis, renal scarring, or parenchymal and functional loss from a single or recurrent UTI. The progression from cystitis to pyelonephritis and the relationship between these entities is difficult to determine, because simple techniques with which to localize the level and extent of urinary tract bacteria are lacking. Both ureteral catheterization and Fairley bladder washout localization techniques are invasive and impractical.[88] Clinical

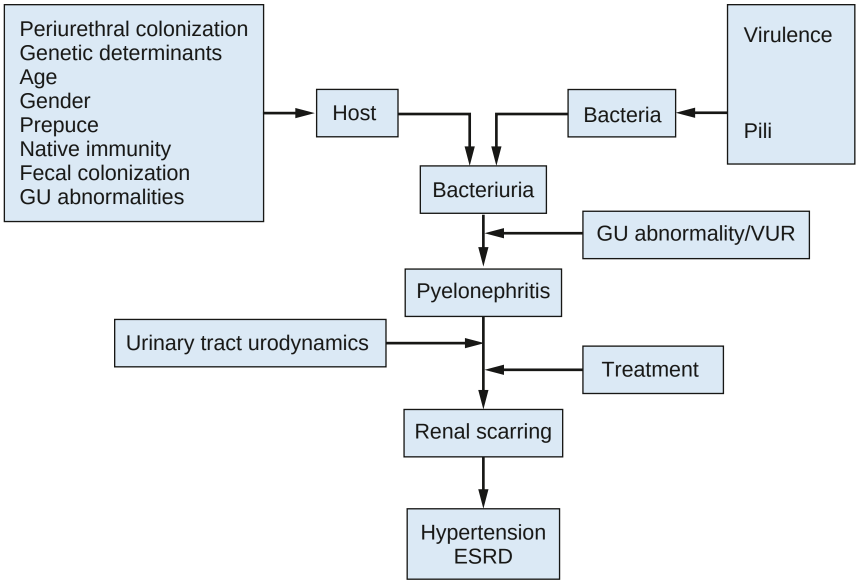


Figure 13-1 Factors that affect the development of bacteriuria and subsequent pyelonephritis, renal scarring, hypertension, and end-stage renal disease (ESRD). Urinary tract urodynamics reflect urinary tract pressures. GU, genitourinary; VUR, vesicoureteral reflux.

symptoms such as fever and flank pain correlate poorly with the location of infection using these upper tract localization studies. In one such study, fewer than half (34/73) of the patients (and most of the pediatric patients) with fever and flank pain had upper tract bacteria, whereas almost 20% (83/473) of those who were asymptomatic had upper tract bacteria.[89]

The discovery that early renal cortical lesions from pyelonephritis can be detected by technetium 99m (Tc^{99m})–labeled DMSA nuclear scanning has advanced knowledge of the natural history of urinary tract bacteriuria.[90-93] Lesions identified on DMSA scans correlated with histopathologic areas of acute renal inflammation in animal studies. When DMSA lesions were used as the standard for diagnosing acute pyelonephritis, about 50% to 86% of children (about 60% of kidneys) with febrile UTIs and other clinical signs were found to have renal involvement.[94-97] About half (40% to 75%) of these lesions persisted on DMSA scans performed 2 months to 2 years later.[94,96] This factor suggests that as many as 40% to 50% of young children who have febrile UTIs suffer renal scarring.

Renal Scarring

Previously, the coarse renal scarring defined radiologically by calyceal deformity and parenchymal thinning over localized or multiple calyces was called "reflux nephropathy." Now that it is clear that such scarring is as likely to occur with or without reflux, this kind of scarring would probably be better termed *pyelonephritogenic* or simply *pyelonephritic scarring.*

With older imaging techniques (before the advent of DMSA), renal scarring was identified in about 17% of school children with screening bacteriuria.[7,70,72] This finding supports Winberg's observation that 4.5% and 17% of children have renal scars on imaging studies after their first and second symptomatic UTI, respectively.[12] Current studies employing DMSA scintigraphy yield almost double the incidence of scarring, so these rates are probably underestimates. Nevertheless, these older data emphasize that children with both covert and symptomatic UTI risk significant renal scarring. Although, by definition, the natural history and pathogenesis of scarring in covert or asymptomatic bacteriuria cannot be known, scars may actually reflect injury from previously undiagnosed bacteriuric episodes and the child's predisposition for recurrent infections.

In most children in whom renal scarring was found on UTI imaging evaluation, the scars were found on the first set of imaging studies and remained unchanged irrespective of the child's future clinical course.[97] It is hypothesized that the young kidney is more susceptible to injury, so that the initial UTI in the neonate or young child (<4 or 5 years old) causes whatever renal damage will occur. This initial response then determines the kidney's future course. This theory is supported by Ditchfield and associates, who found that early scarring in the setting of UTI was twice as likely to occur in children who had their first UTI before 2 years of age rather than later.[98]

On the other hand, scarring may occur in up to 7.3% of children with recurrent or persistent bacteriuria and reflux, with an average age at new scar formation from 7 to 9 years.[95,97,99] Almost all young children with recurrent pyelonephritis suffer renal scarring.[95] Jodal found a direct relationship between the number of episodes of pyelonephritis and the prevalence of renal scarring.[100] Earlier studies also linked new or progressive renal scarring to uncontrolled recurrent UTI and VUR.[101,102] Filly and associates found that, in girls younger than 10 years of age who had recurrent UTI and VUR, renal scars progressed in 43% (17/40) of kidneys, and 13% (2/16) of normal kidneys developed new scars.[101] Some of the scars took up to 2 years from the episode of pyelonephritis to evolve maximally.

Although age may confer some protection from UTI-induced renal scarring, vulnerability for scarring persists at least until puberty (10 to 15 years).[99,102] Studies examining DMSA-detected renal scars suggest that new or progressive renal scarring occurs in older children more commonly than was previously thought. In a recent prospective study, 52 children older than 5 years of age who were admitted with probable acute pyelonephritis were evaluated with DMSA scanning. Cortical scintigraphy revealed renal lesions in 78.8% (41/52) that persisted in 28.2% (9/41) after 3 months' time.[103]

Conversely, in girls with nonobstructive reflux (grades II through IV on International Reflux Grading) who were without recurrent infections, no new renal damage was found with up to 10 years of follow-up.[104] This supports earlier animal and clinical data indicating that, given normal urinary tract urodynamics, VUR alone does not cause further renal damage or impaired renal function.[105-107] No association between VUR and future renal growth or functional impairment has been demonstrated if the urinary tract is otherwise normal and no UTI is realized.[107]

Associated Urinary Tract Abnormalities

Between 5% and 10% of children with UTI have obstructive urinary tract lesions, and an additional 21% to 57% have VUR.[11,12,60,61,63] When only children with pyelonephritis diagnosed with DMSA are examined, 25% to 83% may have VUR, with many studies showing reflux absent in more than half of children with pyelonephritis.[96,108-110]

Children with febrile UTI and reflux are likely to have a defect on DMSA if imaged while sick. Which acute defects will result in scar is still debatable, but the risk of scarring increases with grade of reflux.[109] Older investigations have documented scars in 5% to 20% of kidneys with grade I reflux and in 50% or more of kidneys with grade V reflux.[111-114] Conversely, when renal scarring is examined, about 60% are associated with VUR.[7,70,72] In at least 25% of children, the urinary tract is normal except for the presence of scarring.[108] These data confirm that VUR is only one factor involved in the ascent of bacteria into the kidney and the subsequent risk of renal scarring. No evidence of association between VUR and risk of bacteriuria exists.

Recurrent Urinary Tract Infections

Recurrent UTIs are common, and the natural history was well documented by Winberg and associates.[12] Eighteen percent of neonatal boys and 26% of girls who were younger than 1 year of age when infected developed a recurrent infection, with most of the recurrences occurring within the first year of life; recurrences developing more than 1 year after the initial infection were rare. In contrast, when the initial infection occurred in an older child, more became re-infected (boys 32%, girls 40%). Thereafter, the incidence of infections dropped with each infection-free subsequent year.

Winberg and associates found that the risk of another UTI's developing in a girl within 1 year of the last UTI was proportional to the number of previous infections (i.e., the more infections a girl has had, the more likely she is to get another). Their data showed that the risk of getting another UTI within 1 year after a first UTI was more than 25%; with two previous UTIs, the risk was greater than 50%, and with three previous UTIs, it was almost 75%.[12] This recurrence rate was the same regardless of whether the initial infection was symptomatic or asymptomatic, pyelonephritis or cystitis. In fact, about one third of the recurrences were asymptomatic. Analysis of UTI *E. coli* isolates using newer techniques suggests that recurrent UTIs in infants are more likely to be re-infections with the same organism from bowel, rather than new organism re-infections.[115]

Voiding Dysfunction and Constipation

Symptoms of nocturnal and diurnal incontinence are common in children with recurrent UTI. Epidemiologic studies have shown that nocturnal enuresis alone is not associated with UTI. On the other hand, diurnal enuresis or a combination of diurnal and nocturnal enuresis is associated with pediatric UTI, even when the enuretic episodes are as infrequent as once a week.[116] Interestingly, almost 20% of children who experienced a recurrent UTI developed new diurnal enuresis, persisting for as long as 12 months, even though the urine remained clear.[117]

Urodynamic testing of otherwise radiologically normal children with recurrent UTI and incontinence showed abnormal cystometry and voiding patterns.[118-125] In 35 such children, Bauer and associates[120] found that 12 (34%) had normal filling cystometry, 9 (26%) had large hypotonic bladders, 9 (26%) had small-capacity hypertonic bladders with increased intravesical filling pressure and sustained uncontrolled detrusor contraction at a low volume, and 5 (14%) had hyperreflexic bladders showing uninhibited detrusor contractions during filling. Voiding dysfunction has also been described, with staccato urinary flows, increased pelvic floor activity during voiding, and resulting incomplete bladder emptying.[116,120,124-126]

Voiding dysfunction in neurologically normal children also appears to influence the natural history and treatment of VUR. Koff and coworkers[127] examined 143 children with primary VUR and noted that 66 (43%) had voiding dysfunction defined by evidence of bladder instability, infrequent voiding, the Hinman syndrome, and constipation. Of these 66 children, 54 (82%) underwent reimplantation secondary to breakthrough infections, compared with only 18% of those who were without voiding dysfunction. Of 70 children who had breakthrough UTI, voiding dysfunction was present in 54 (77%) and absent in 16 (23%). The authors also noted that low-grade VUR required, on average, 1.6 years longer to resolve in children with voiding dysfunction.

Bowel dysfunction with constipation is commonly seen in children with bladder filling and voiding dysfunction.[128,129] When 47 girls with normal urinary tracts but recurrent UTIs (with or without incontinence) and cystometry-proven bladder instability were studied by digital rectal examination and rectal manometry, all had signs of functional constipation. Importantly, these findings were present even when constipation or encopresis was specifically denied. Others have not found constipation or daytime incontinence to be predictive of recurrent UTI.[130]

Although these findings do not establish causality between UTI and voiding dysfunction, UTI may initiate symptoms of bladder dysfunction with variable persistence. In some situations, treatment of constipation or voiding abnormalities, or both, has resulted in decreased frequency of urinary infections[118-121,125,126,128,131-133] and this possible relationship should be considered in the management of VUR[127,134] even though the association is unclear.[135] The data suggest that bacteriuria may provoke abnormal detrusor activity.

PATHOGENESIS OF RENAL SCARRING

The pathogenesis of renal scarring involves widespread changes that alter urinary tract urodynamics.[136,137] Animal studies have demonstrated that UTI can cause abnormally elevated renal pelvic pressures, especially if VUR is absent.[138] This supports the clinical observation that infection with certain so-called pyelonephritogenic *E. coli* may cause the temporary ureteral dilation seen in children with acute pyelonephritis and otherwise normal upper collecting systems.[139]

Renal scarring appears to be affected by at least five factors: intrarenal reflux, urinary tract pressure, host immunity, age, and treatment. Hodson[140] and Rolleston and coworkers[141] found that areas of renal scarring were associated with foci of intrarenal reflux (pyelotubular backflow) observed on voiding cystourethrography (VCUG) in children younger than 4 years of age who had VUR. Examination of these calyces revealed fusion of adjacent papillae, which resulted in opening of the papillary ducts at right angles rather than at oblique angles more resistant to reflux.[142] These compound papillae were found most commonly at the renal poles, the areas in which clinical renal scarring is most frequently observed clinically.[143] The common patterns of scarring are shown in Figure 13-2.

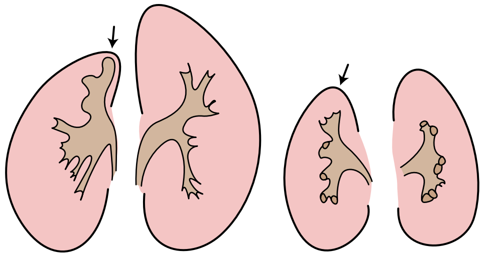
Whereas animal studies show that renal scarring occurs only when VUR and intrarenal reflux are associated with bacteriuria,[106] renal scarring may occur with VUR alone (without UTI) if there is an obstructed, high-pressure bladder.[105,144]

Renal infection stimulates both humoral and cellular immune responses. In rat models of pyelonephritis, maximal renal suppuration and exudation with inflammatory infiltration occurs 3 to 5 days after the infection starts.[145-150] During the acute inflammatory infiltration, granulocytic aggregation may cause vascular occlusion and ischemia with elevation of renin levels.[151,152] Bactericidal activity of the neutrophils and the release of enzymes, superoxide, and oxygen radicals may cause the renal tubular damage observed in pyelonephritis.[153] The resulting proximal and distal tubular dysfunction causes reduced urinary concentrating ability.[154] With the increased fractional sodium excretion, there is decreased phosphate reabsorption and increased excretion of low-molecular-weight protein.[155] Clinical studies have correlated decreased renal concentrating capacity with severity of renal scarring (bilateral scarring is worse than unilateral).[156]

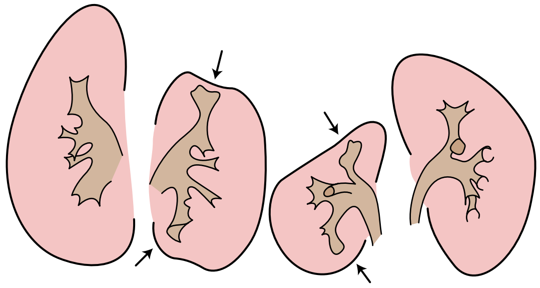
If antimicrobial treatment is started within the first days of infection, the acute suppurative response to the bacteria may be minimized, and renal scarring may be decreased or prevented.[145,147,149,150] Clinical studies have shown that the larger cortical defects correlate with a longer delay in treatment and longer length of illness.[109] In preliminary studies on animals, reduction of inflammation through the use of corticosteroids, ibuprofen, or inhibition of superoxide production decreases renal tubular damage and scarring.[148,157-159] Further research is required to elucidate treatment efficacy.

Clinical studies confirm that young children are at greatest risk of renal scarring from bacterial pyelonephritis. Several factors contribute to this finding. First, the neonatal kidney may respond to urinary back-pressure (the water hammer effect) in different ways and at different thresholds than the adult kidney. Autopsy studies on normal neonates (children <1 month old) revealed that intrarenal reflux into compound calyces may be created at low pressures of 2 mm Hg, whereas the same reflux in a 1-year-old child occurs at 20 mm Hg. Furthermore, in autopsy studies of children younger than 12 years of age, intrarenal reflux was found to occur in all calyces, even simple ones, at 50 mm Hg.[159] This suggests that physiologically normal urinary intrapelvic pressures in adults or older children may be abnormally high in neonates, and ureteral and pelvic smooth muscle dysfunction may further exacerbate this effect.[138]

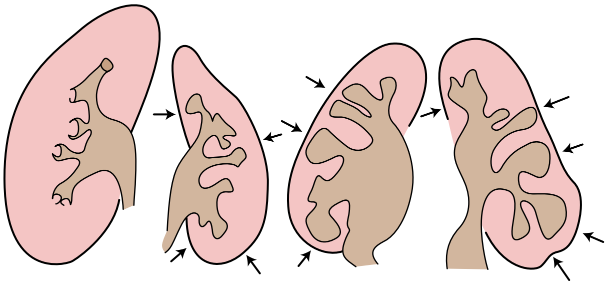
Second, very young children have an incompletely developed immune and neurologic system. A depressed or incompletely mature immune system may allow bacteria to colonize the bladder and kidney more easily because of decreased local and systemic defenses. It may also kill or eliminate bacteria less efficiently once bacteriuria occurs. Moreover, neurologic immaturity of the bladder may allow frequent uninhibited bladder contractions to transmit their pressures to the upper tracts in even the apparently normal child.[160] Bacteriuria combined with reflux in such a child may result in greater susceptibility to renal damage.



1. Upper pole scarring



2. Upper and lower pole scarring



3. Generalized scarring

Figure 13-2 Common areas of renal scarring characterized by parenchymal thinning over a deformed calyx, as determined from intravenous pyelograms. The extent of scarring may be related to single polar scars; multiple areas of upper, lower, and medial scars; or generalized scarring, as depicted. (Reproduced by permission from Hodson CJ. Natural history of chronic pyelonephritic scarring. *BMJ.* 1965;2:191-194).

Third, neonatal UTI symptoms are often vague and nonspecific, leading to delayed or inadequate treatment.[161] This delay may result in a kidney that responds to bacterial invasion with an inflammatory response characterized by vascular granulocytic aggregation and hypoperfusion with subsequent scarring and loss of renal parenchyma.[12]

Recently, research has focused on the effects of the renin-angiotensin system on renal scarring. It is hypothesized that increased angiotensin II may increase scarring through its hemodynamic as well as its growth-related and prosclerotic effects. Studies provide evidence that the homozygous deletion polymorphism (DD genotype) that is associated with increased activity of the renin-angiotensin system and angiotensin II may be a genetic susceptibility factor contributing to renal scarring.[162,163] Ozen and associates[163] found that 28 (80%) of 35 patients with a DD genotype developed scarred kidneys on DMSA. Of 53 patients with scarring, 28 children possessed the DD genotype. Nevertheless, no association between DD genotype and hypertension or decreased renal function was observed. Recent studies have shown conflicting data, however, and further investigation is warranted.[164]

PYELONEPHRITOGENIC HYPERTENSION

The incidence of hypertension in childhood ranges from 1% to 11% depending on age and sex. Pyelonephritic scarring associated with UTI remains the most common cause of hypertension in childhood.[165] In particular, approximately 10% to 20% of children with pyelonephritogenic nephropathy will develop hypertension in the future.[166-171]

Wallace and associates found that 12.8% of 141 patients with urinary infections and surgically corrected VUR developed hypertension during the first 10 years of follow-up.[167] Of those with renal scarring, 17% became hypertensive during follow-up. In another series with 4 to 20 years of follow-up, 30% of children who were found to have renal scars developed infection-related hypertension; 13% (11/83) had initial hypertension.[168] Others have reported that 23% of children with nonobstructive focal renal scarring developed hypertension after 27 years, and, of these, 10% developed ESRD.[169] In these series, hypertension was independent of the degree of scarring. More recent examination of 24-hour ambulatory blood pressure measurements suggested that hypertension measured in this fashion correlates directly with the degree of reflux nephropathy. Nocturnal hypertension was the most sensitive indicator, but whether it is predictive of daytime hypertension has not been validated.[172]

The etiology of pyelonephritogenic hypertension is poorly understood. It is likely that the renin-angiotensin system is involved. Although some evidence of elevated plasma renin activity exists, no direct correlation of blood pressure with degree of scarring, plasma renin activity, or creatinine has been found.[173] Further indirect evidence of the role of renin in pyelonephritogenic nephropathy has been the successful treatment of hypertension with agents specifically aimed at blocking the renin-angiotensin system.

DIAGNOSIS

Clinical Symptoms

UTI is a common cause of pediatric bacterial infection[174-176] and accounts for 4.1% to 7.5% of febrile illnesses.[177,178] Early diagnosis of UTI and rapid treatment with antimicrobial agents are essential in preventing renal damage. However, the clinical symptoms of UTI are variable and differ by age. In infants, the symptoms of UTI may be difficult to discern, with the only signs being those of generalized illness—fever, irritability, poor feeding, vomiting and diarrhea. Moreover, febrile infants who are not suspected of having a UTI are as likely to have a urinary source of infection as those who are (5.1% versus 5.9%).[176] It has been recommended that testing for UTI be performed for all infants younger than 8 weeks of age who present with asymptomatic jaundice.[179] In febrile infants, neither clinical symptoms nor laboratory tests can be used to presume or eliminate the likelihood of a UTI, even if other sites of infection are suggested clinically.[174]

The manifestations of UTI symptoms in young children (<2 years) may be similar to those in infants. To avoid unnecessary urine cultures, clinical guidelines have been proposed. When evaluating febrile young girls, urine cultures should be obtained if two of the following five parameters are present: (1) age younger than 12 months, (2) white race, (3) absence of other fever source, (4) fever greater than 39° C, and (5) fever lasting 2 days or longer. If followed, these parameters would predict UTI with a sensitivity of 95% and a specificity of 31%, avoiding 30% of unnecessary cultures.[180]

In older children, dysuria, suprapubic or urethral pain, frequency, intermittent voiding dysfunction, and incontinence may be seen. In children with known genitourinary abnormalities and nonspecific symptoms, it is critical to consider a UTI.

Signs

There are no signs specific to UTI in the infant or child; nevertheless, physical examination should focus on findings that, when present or absent, will be diagnostically helpful. Pertinent areas include the flank for renal masses or pain; the abdomen for masses or pain; the perineum for ectopic ureteral openings, prolapsed ureterocele or urethra, or urethral discharge; the sacral area for back scars, dimple, pits, or fat pad that could be associated with tethered cord or dysraphism; and the testes for masses, epididymitis, and tenderness.

Diagnostic Tests

Urinalysis and Culture

COLLECTION OF THE URINARY SPECIMEN

The diagnosis of UTI is predicated on obtaining a good urinary specimen, which can be difficult in children. Routinely, there are four ways that urinary specimens are obtained in children. In order of least to most reliable for UTI diagnosis, they are (1) plastic bag attached to the perineum ("bagged specimen"), (2) midstream void, (3) catheter specimen, or (4) a suprapubic bladder aspirate.[181] A plastic bag specimen, despite thorough skin cleansing, usually reflects the perineal and rectal flora and can yield false-positive results. Although a midstream voided specimen in a circumcised boy, older girl, or older uncircumcised boy who can retract his foreskin may reliably represent the urine, such specimens obtained in young girls and uncircumcised boys usually reflect periurethral and preputial organisms and cells. A catheterized specimen is reliable if the first portion of urine, which may contain urethral organisms, is discarded and the specimen is taken from later flow through the catheter; however, catheterization can be traumatic and can potentially introduce urethral organisms into the sterile urinary tract.[182-184]

The most reliable urinary specimen for culture is obtained by suprapubic bladder aspiration. This can be performed safely in children and even in premature infants with a full bladder by cleansing the skin and percutaneously introducing a 21- or 22-gauge needle 1 to 2 cm above the pubic symphysis until urine is obtained by aspiration into a sterile syringe.[183] Because the urine does not cross the urethra, urethral and periurethral organisms are absent, and skin contamination should be nil. Organisms present in a suprapubic aspirate are pathognomonic of bacteriuria.[185]

The main drawback of suprapubic aspiration is that needle aspiration may be distasteful or inconvenient to the older child, parent, or even physician, and these considerations may be important.[186] The application of a local anesthetic cream, such as topical lidocaine and prilocaine, provides excellent analgesia prior to suprapubic aspiration in young children.

In a child who is not yet toilet trained, only a catheterized or needle-aspirated specimen is acceptable for diagnosis. Assuming that the prevalence of UTI is 2%, the false-positive rate for bagged specimens is approximately 93%, based on a summary of the literature.[161] Under special collection circumstances, when the perineum is cleaned well and the bag is removed and processed promptly after voiding, a "bagged" specimen or even a diaper specimen showing no growth may be useful in *eliminating* bacteriuria as a possibility.[187] Plastic bag specimens are unacceptable for diagnosis of UTI in high-risk populations and in infants younger than 2 months old.[174]

URINALYSIS

The gold standard for the diagnosis of UTI is quantitative urinary culture. Yet, controversy exists regarding the interpretation of urinalysis and culture results. Four determinations from the urinalysis may be useful in supporting a diagnosis of UTI: (1) microscopic urinary examination for white blood cells (WBCs), called "pyuria"; (2) microscopic urinary examination for bacteria; (3) urinary leukocyte esterase; and (4) urinary nitrite (Table 13-2).

The microscopic identification of bacteria in the urine is more sensitive and more specific for diagnosing UTI than is identification of pyuria.[188,189] The finding of urinary sediment red cells and WBC casts is even less reliable. Hoberman and associates proposed the use of an "enhanced urinalysis," in which an uncentrifuged specimen is examined for WBCs and a Gram stain is performed for bacteria, with pyuria defined as the presence of greater than 10 WBCs/mm^3.[190] For identifying positive urine cultures, those with greater than 50,000 colony-forming units (CFU) per milliliter, this method produced a sensitivity of 84%, compared with 66% for standard urinalysis.

Urinary leukocyte esterase detects urinary esterases produced by the breakdown of WBCs in the urine, yet WBCs may not be present with the infection. The test may be less reliable in infants.[191] The urinary nitrite test measures dietary nitrates that are reduced to nitrite by many gram-negative urinary bacteria and has a high specificity. (Most gram-positive bacteria do not perform this reduction.) A serious drawback of this test is that the bacterial reduction to nitrite may take several hours; therefore, this test is most useful on first morning voided specimens. Although both tests may be performed by dipstick in the urine, the tests are more unreliable when the bacterial count is lower than 100,000 CFU/mL.

No combination of urinary tests meets the gold standard of culture, but several tests may help predict patients in whom culture will be positive. In febrile children younger than 2 years of age, Hoberman and coworkers found that catheter-obtained specimens had a positive predictive value for UTI diagnosis of 88.3% if microscopic examination showed bacteria and greater than 10 WBC/mm^3, but they emphasized that UTI in these children is best defined by a urinary leukocyte count of greater than 10 WBCs/mm^3 and greater than 50,000 CFU/mL on culture.[191] In a more general child population, others have shown that, when urinary specimens are properly collected and promptly processed, positive leukocyte esterase and nitrite tests, in combination with microscopic confirmation of bacteria, have 100% sensitivity for detection of UTI. When all tests (or leukocyte esterase and nitrite tests) are negative, the negative predictive value approaches 100%.[192,193] In febrile children 3 to 24 months old, a risk-benefit analysis based on the current literature, which had the goal of preventing the majority of cases of UTI-related ESRD and hypertension, concluded that both urinalysis and culture are needed to optimize prevention.[161,194] The arguments for and against relying on urinalysis characteristics for the presumptive diagnosis of a UTI were well summarized by Lohr.[189]

URINE CULTURE

Defining urine culture parameters that result in a "significant" UTI is challenging. As already discussed, the technique by which the urinary specimen is collected correlates with its reliability for UTI diagnosis (Table 13-3).[195] Classically, a clinically significant UTI has greater than 100,000 CFU/mL in a voided specimen.[196] However, other studies have shown that 10,000 or fewer organisms on a voided specimen may indicate a significant UTI.[197,198] In febrile children younger than 2 years of age, Hoberman and associates showed that greater than 50,000 CFU/mL in catheterized specimens constituted a significant UTI.[191] It should be noted, however, that in most of these studies only 0.001 mL of urine was cultured, so the lower limit of detection was 1000 CFU/mL. Any organisms cultured from a suprapubic aspirate specimen are significant. Hoberman and Wald proposed that only urine specimens with pyuria, as defined by the "enhanced urinalysis," and those from children receiving antimicrobial therapy should be cultured, in order to reduce costs.[178]

Table 13-2 Sensitivity and Specificity of a Positive Result on Urine Dipstick Tests and Microscopic Urinalysis

Test	Sensitivity, % (Range)	Specificity, % (Range)
Leukocyte esterase	83 (67-94)	78 (64-92)
Nitrite	53 (15-82)	98 (90-100)
Leukocyte esterase *or* nitrite positive	93 (90-100)	72 (58-91)
Microscopy: white blood cells	73 (32-100)	81 (45-98)
Microscopy: bacteria	81 (16-99)	83 (11-100)
Leukocyte esterase *or* nitrite *or* microscopy positive	99.8 (99-100)	70 (60-92)

Reprinted with permission from American Academy of Pediatrics, Practice Parameter: The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics*. 1999;103:843-852.

Imaging Studies

Imaging evaluation is important to the diagnosis and management of UTI with the goal of altering or preventing further morbidity. Radiologic imaging can be used to (1) evaluate and localize the acute urinary infection, (2) detect renal damage from the acute infection, (3) identify genitourinary anatomy that increases the risk of future renal damage from infection, and (4) evaluate changes in the urinary tract over time. An algorithm for deciding which studies are necessary in a child with a presumptive or diagnosed UTI is provided in Figure 13-3. It should be kept in mind that imaging studies are recommended only if their findings may change clinical management. A detailed review of the relevant imaging studies can be found in Chapter 3.

RADIOLOGIC STUDIES IN THE ACUTE SETTING

If the initiation or duration of antimicrobial therapy hinges on localizing an infection to the kidney, an acute imaging study can be performed. This could be helpful for children in whom urine culture data is indeterminate. A DMSA scan performed when the child presents with symptoms may show whether acute renal inflammation in occurring in the kidney with hypoperfusion defects or visible renal swelling. The uptake defects may appear wedge-shaped in lateral or polar areas or scattered within the kidney.[199]

In a study of 175 children with a febrile UTI, a DMSA scan obtained within about 14 days of presentation was abnormal in only 42% of patients.[200] Furthermore, acute studies of the

Table 13-3 Culture Criteria for Diagnosis of Urinary Tract Infection

Method of Collection	Colony Count (Pure Culture)	Probability of Infection (%)
Suprapubic aspiration	Gram-negative bacilli: any number Gram-positive cocci: more than a few thousand	>99
Catheterization	$>10^5$	95
	10^4 to 10^5	Infection likely
	10^3 to 10^4	Suspicious; repeat
	$<10^3$	Infection unlikely
Clean-voided (male)	$>10^4$	Infection likely
Clean-voided (female)	Three specimens: $>10^5$	95
	Two specimens: $>10^5$	90
	One specimen: $>10^5$	80
	5×10^4 to 10^5	Suspicious; repeat
	10^4 to 5×10^4	Symptomatic; suspicious; repeat
	10^4 to 5×10^4	Asymptomatic; infection unlikely
	$<10^4$	Infection unlikely

Reprinted with permission from Hellerstein S. Recurrent urinary tract infections in children. *Pediatr Infect Dis.* 1982;1:271.

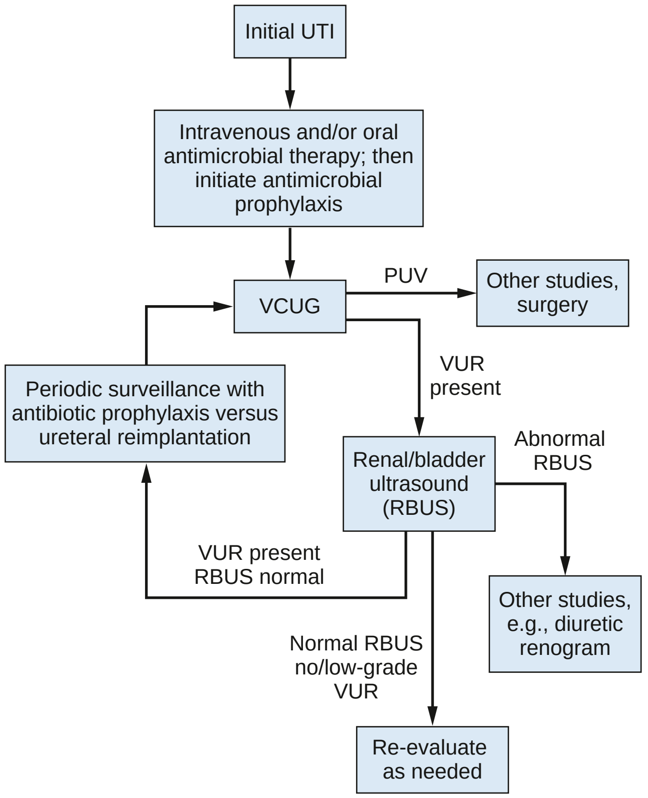

Initial UTI
Intravenous and/or oral antimicrobial therapy; then initiate antimicrobial prophylaxis
VCUG
PUV
Other studies, surgery
VUR present
Periodic surveillance with antibiotic prophylaxis versus ureteral reimplantation
Renal/bladder ultrasound (RBUS)
Abnormal RBUS
VUR present RBUS normal
Other studies, e.g., diuretic renogram
Normal RBUS no/low-grade VUR
Re-evaluate as needed

Figure 13-3 Flow diagram of possible imaging studies used to evaluate infants and children with urinary tract infection (UTI). PUV, posterior urethral valves; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

kidney may overestimate renal size, because of initial edema, and underestimate the degree of renal scarring, because mature renal scars may take up to 2 years to be seen by certain imaging techniques.[101,201-204] Finally, if a child is severely ill and has strong presumptive clinical evidence of UTI, and antimicrobial treatment will be started regardless of radiologic findings, DMSA will not change clinical management and is not recommended.[205]

Circumstances such as a poor response to appropriate antimicrobial drugs after 3 to 4 days, an unusual infecting organism (tuberculosis or a urea-splitting organism such as *Proteus*), newly diagnosed uremia, known partial obstruction, nonfunctioning or poorly functioning renal units, history of papillary necrosis, or a neurogenic bladder may warrant acute or early urinary tract imaging. Ultrasonography and abdominal computed tomography (CT) provide excellent imaging of the kidney to exclude the possibility of a renal abscess and allow concurrent therapeutic procedures to be performed if necessary.

INITIAL AND FOLLOW-UP IMAGING EVALUATIONS

Controversy exists as to whether studies should be performed after the first UTI or after a recurrent episode of infection. Assuming that obstructive lesions are found in 5% to 10% of children and reflux occurs in 21% to 57%,[11,70-72] early detection of these abnormalities merits full urinary tract imaging evaluation after the first infection in young children. This usually consists of some form of renal and urinary tract evaluation and VCUG. The evaluation should commence after the initial UTI has been adequately treated, and the child should be maintained on antimicrobial prophylaxis until the evaluation is complete.

If the initial imaging evaluation of the child with an initial UTI is negative, no further studies are necessary. If studies during the acute infection reveal edema or hypoperfusion defects with normal collecting systems, a follow-up study should be obtained to evaluate for renal scarring and growth problems. If a child has recurrent symptomatic pyelonephritis and no reflux was found on previous fluoroscopic VCUG, a nuclear VCUG may be more sensitive at revealing reflux, although less likely to define it.[206,207]

VOIDING CYSTOURETHROGRAPHY

The VCUG is the most important examination in assessing VUR in children. The VCUG may be performed either with fluoroscopy and iodinated contrast or with nuclear imaging agents (usually Tc^{99m}-pertechnetate) using similar techniques (direct radionuclide cystography, or RNC). Fluoroscopic and nuclear VCUG provide different information and, as such, have different indications. The traditional fluoroscopic VCUG can show urethral and bladder abnormalities as well as VUR. The RNC may be more sensitive for reflux detection, but it poorly evaluates the urethra and does not allow grading of reflux. Detection of VUR by either fluoroscopic or radionuclide VCUG may rely on the child's ability to void and the proper performance of certain technical aspects of the study, such as filling the bladder to capacity.[207-209] The radionuclide VCUG should not be used to evaluate first infections in infants or young boys in whom risk of genitourinary abnormality is high and urethral visualization important, nor in any child in whom imaging resolution of the lower urinary tract is important. The radionuclide VCUG may be most useful for VUR screening, for evaluation of the UTI in older children who have a lower risk of reflux, or for follow-up reflux evaluation.[210]

The main advantage of RNC has been the lower radiation exposure: 1 to 5 mrad (ovarian dose) instead of 27 to 1000 mrad (previously reported ovarian exposure depending on equipment).[210,211] With modern imaging technology and a tailored examination, however, the fluoroscopic VCUG has been done with exposures of 1.7 to 5.2 mrad.[212] Indirect radionuclide VCUG has been proposed as part of a renal imaging study and avoids catheterization by allowing the bladder to fill with tracer cleared by the kidneys. However, because it detects only about 60% of the reflux cases, compared with direct VCUG, this is not recommended.[177]

The VCUG may be performed as soon as the urine is sterile and bladder irritability is absent with return to normal capacity. Studies have shown that UTIs do not cause reflux.[210] Whether the VCUG is done during treatment or a few weeks after the UTI is unimportant, so long as the child has normal renal function, responds rapidly to antimicrobial treatment, and is maintained on prophylactic antimicrobial treatment to keep urine sterile in the interval between the herald infection and the radiologic evaluation.

Subsequent imaging should be tailored to the results of the VCUG.[213] In most cases, a kidney and bladder ultrasound study complements the VCUG well, detecting other urinary tract structural abnormalities such as dysplasia or obstruction.[207,214-217] However, some argue that the widespread use of antenatal ultrasound detects many of these abnormalities, and ultrasound should be used selectively rather than routinely in the initial evaluation of a febrile UTI.[69] Further prospective study in a large, varied patient population is necessary to clarify this issue. Finally, if VUR appears to be the primary diagnosis, DMSA scintigraphy with single-photon emission computed tomography (SPECT) or three-dimensional renal magnetic resonance imaging (MRI) may be the most useful studies with which to detect renal scars.

RENAL AND BLADDER ULTRASONOGRAPHY

Routine renal ultrasonography is not as sensitive as DMSA at detecting the subtle changes associated with acute UTI.[177,218-221] Ultrasonography may show enlarged swollen kidneys, focal enlargement from edema and inflammation (focal pyelonephritis or lobar nephronia), and ureteral widening,[201,203,204,207,213-217,222] but even color Doppler sonography has poor sensitivity for detecting the small areas of inflammation and resulting hypoperfusion that are seen on DMSA.[223] Renal and bladder sonography is, however, more likely to detect perinephric fluid collections or anatomic abnormalities, especially those involving urinary tract dilatation, than either DMSA or intravenous urography (IVU).[219]

NUCLEAR RENOGRAPHY

Nuclear scintigraphy can detect areas of acute renal inflammation and chronic scarring, and this capability has changed imaging of pediatric UTIs. DMSA is clearly more sensitive than renal sonography or even IVU at detecting renal scarring. Approximately 60% of injected Tc99m-DMSA is bound to proximal tubular cells and is subsequently secreted slowly in the urine, thus delineating the cortical anatomy. After the acute episode is healed, the scans may show (1) a normal pattern, (2) generally diminished uptake and small kidney volume, (3) diminished uptake in the medial kidney, or (4) polar defects with diminished uptake in the renal poles.[199] Because recurrent pyelonephritis appears to occur in the same areas, it may be difficult to differentiate new from old or progressive renal scarring unless serial studies have been performed.[96,218] Finally, for children in whom severe renal scarring has occurred, the radionuclide renogram has been found to give an accurate estimate of relative function, even in young children.[224-226]

OTHER RADIOLOGIC STUDIES

Historically, the IVU with renal tomograms was used to identify renal scarring, but in most situations DMSA scintigraphy has assumed the role of the IVU. Of course, IVU still identifies collecting system abnormalities with more detail than either DMSA or ultrasonography. Currently, IVU does not play a role in the initial evaluation of a UTI, but it may be useful in patients with bacterial persistence.

No extensive studies have directly compared the sensitivity and specificity of DMSA and CT or MRI for detecting renal lesions in acute or chronic pyelonephritis. However, in one study comparing the use of MRI and nuclear imaging techniques in a cohort of 37 children with acute pyelonephritis, MRI was found to detect more acute pyelonephritic lesions with superior interobserver reliability when compared to DMSA scans.[227,228] However, for routine acute UTI evaluation, neither modality is practical. In children with complicated infections, either CT or MRI may be useful for defining renal abnormalities and extent of disease and either is probably as sensitive as DMSA for detecting renal scars.[229,230] Recent MRI protocols provide excellent definition of the renal cortex and collecting system and accurate assessments of function.[231]

MANAGEMENT

Treatment of Acute Urinary Tract Infection

The therapeutic goal of management in pediatric UTI is to minimize acute morbidities, prevent urosepsis, and minimize the risk of future renal damage from subsequent infections. Rapid recognition of a UTI and rapid, appropriate antimicrobial treatment are keys to preventing renal damage. Treatment varies depending on the child's age and severity of illness.

When treatment of UTI is considered, infants younger than 90 days are usually considered separately from older children. Children younger than 90 days of age are more likely to have their course of disease change rapidly because of their physiology and incompletely developed immune system.[232] The child younger than 2 to 3 months who has a presumptive UTI and looks systemically ill, has a fever or flank or abdominal pain, is unable to take fluids, or is immunocompromised should be treated with parenteral broad-spectrum antimicrobial agents (e.g., aminoglycoside and ampicillin, third-generation cephalosporin, aminoglycoside, and cephalosporin; Table 13-4) and

Table 13-4 **Treating Pediatric Urinary Tract Infections: Common Antimicrobial Agents**

Parenteral Agents	Oral Agents
Aminoglycosides	**Cephalosporins**
Gentamicin	**First-Generation**
Tobramycin	Cephalexin
Cephalosporins	Cefadroxil
Cefazolin	**Second-Generation**
Cefotaxime	Cefaclor
Ceftriaxone	Cefuroxime axetil
Ceftazidime	Cefprozil
Penicillins	Loracarbef
Ampicillin	**Third-Generation**
Ticarcillin	Cefixime
Piperacillin	**Penicillins**
	Ampicillin
	Amoxicillin
	Clavulanate/clavulanate
	Sulfonamides
	Sulfisoxazole
	Trimethoprim-sulfamethoxazole
	Other Agents
	Nitrofurantoin
	Ciprofloxacin*, Levofloxacin*

*Currently, safety and effectiveness of these quinolones in children younger than 18 years old has not been established.

considered for hospitalization. For this patient population, particularly those who are 30 days of age or younger, consideration must be given to antimicrobial coverage of *Listeria monocytogenes* (perinatally acquired) and *E. faecalis* (usually postnatally acquired), for which ampicillin provides coverage, thus making ampicillin and gentamicin recommended at this age.[233] Whereas those younger than 1 month are most often hospitalized for treatment, UTI in those between 30 and 90 days old has been managed on an outpatient basis, depending on the child's clinical status and the presence of a reliable follow-up plan.

In appropriate infants and young children with presumptive UTI who are maintaining oral hydration and have cooperative, reliable parents with whom daily contact is possible, outpatient therapy may be offered. Third-generation cephalosporins, such as ceftriaxone, allow once-daily outpatient parenteral therapy.[234,235] Most of these third-generation cephalosporins have a broad spectrum with high serum levels, treat even *Enterobacter* species and some *Pseudomonas aeruginosa*, and conveniently require only once- or twice-daily dosing. Several studies have shown that once-daily parenteral administration of gentamicin or ceftriaxone in a day treatment center is safe, effective, and cost-effective in children with UTI.[234,236,237] However, *Enterococcus* species are still resistant to most third-generation cephalosporins.

Usually, parenteral treatment is continued for 48 to 72 hours, until the child is afebrile, clinically improving, and taking fluids. Antibiotic therapy can then be tailored based on bacterial sensitivities, and the patient can be switched to an appropriate oral antimicrobial agent that attains adequate serum levels. Analysis has shown that no follow-up urinary culture after 48 hours is required if the organisms are sensitive to the antibiotic selected.[238] Although the duration of treatment is debatable, in most studies involving treatment of febrile UTIs in young children the total duration of therapy has extended from 7 to 10 days.

Older infants and young children who are capable of taking fluids and oral medicines may be treated with an antimicrobial agent that has a broad spectrum for genitourinary pathogens (see Table 13-4). The newer oral cephalosporins have good gram-positive and gram-negative treatment spectrums with convenient dosing schedules. In a multicenter randomized clinical trial, oral cefixime appeared to be as effective as initial intravenous cefotaxime in children 1 to 24 months of age with febrile UTI.[239] However, many *Enterococcus*, *Pseudomonas*, and *Enterobacter* species are resistant to cephalosporins.[240-243]

The newer quinolones are useful because of their broader antimicrobial spectrum and special activity against *P. aeruginosa*, but in children use of this drug is limited at this time because of studies showing quinolone-induced cartilage toxicity in young animals. With careful monitoring, limited quinolone usage has shown no cartilage-related toxicities. In 2005, the quinolones were not yet approved for the treatment of pediatric UTIs, but clinical trials are examining pediatric safety and efficacy issues. Certain clinical situations have prompted more widespread, off-label use in children. An abnormal urinary tract with a complicated UTI with *P. aeruginosa* may be a potential indication for usage.[244] However, quinolone-resistant gram-negative bacteria are emerging in the nosocomial and outpatient setting due to the widespread use of this antibiotic class in the adult population. Local antibiotic susceptibility patterns should be consulted and updated routinely. Finally, because nitrofurantoin attains high urinary concentrations and low serum concentrations, it is a poor choice to treat any severe systemic and renal infection but is ideal for treating a bladder UTI.

In school-age children who do not appear systemically ill and have a "clinically uncomplicated bladder infection," many oral broad-spectrum antimicrobial agents that are well tolerated will cure the UTI in a course of 3 to 5 days. There are no advantages to longer therapy.[245-248] In some of these children, single-dose treatment, particularly with intramuscular aminoglycoside, may be curative.[249,250] However, in unselected children, some with complicated UTI, single doses may not be quite as effective as 3 to 5 days of treatment.[250,251]

After this acute treatment, the child should be started on a daily prophylactic antimicrobial agent until full radiologic evaluation of the urinary tract may be conveniently performed in the next days to weeks.

Treatment of Asymptomatic Bacteriuria

Infections that are asymptomatic, as designated by Savage and colleagues,[252] and are found only on screening urinary culture when a child is being examined for reasons unrelated to urinary infection nevertheless represent either first infection or recurrent infection and mark host susceptibility to bacteriuria. Patients with asymptomatic infections who are diagnosed on screening urinary cultures are often found to have symptoms related to the lower urinary tract when carefully interviewed. When imaging studies are obtained, about 50% of these children have normal urinary tracts as defined by IVU and VCUG.[252,253] Controversy exists as to whether asymptomatic bacteriuria should be treated.[254] Although the majority of infants who have asymptomatic bacteriuria may clear their bacteriuria without treatment,[100] other investigators have found that only about 30% of school-age girls clear their infections

Table 13-5 Indications for Urinary Tract Prophylaxis

Vesicoureteral reflux
Recurrent infections with normal urinary tract
Awaiting radiologic evaluation after urinary tract infection
Unstable urinary tract abnormality (e.g., partial urinary tract obstruction)
Urethral instrumentation
Immunosuppression or immunocompromise
Infants with first urinary tract infection before 8-12 wk of age

spontaneously without treatment.[255,256] Whether they are treated when diagnosed or not, the majority of these girls have or will develop persistent infections or re-infections.[7,100,255]

The bacterial species responsible for asymptomatic bacteriuria may be less pathogenic. For example, the strains of *E. coli* causing asymptomatic bacteriuria may exhibit self-agglutination and loss of surface antigens.[68,257] Some studies have suggested that urinary tract colonization with a strain of *E. coli* causing asymptomatic bacteriuria may prevent colonization with an *E. coli* that can cause symptoms, so that treatment may actually lead to later acute symptomatic pyelonephritis.[68,258,259] Therefore, for difficult cases of recurrent, truly asymptomatic infection, follow-up without further antimicrobial treatment should be considered.

Antimicrobial Prophylaxis

Because renal scarring and damage have been shown to occur only in the presence of infection, the goal of antimicrobial prophylaxis is to sterilize the urine and prevent infection.[260] Urinary prophylactic antimicrobial agents are effective to varying degrees in preventing bacteriuria under certain circumstances. In children, these agents are most commonly used to prevent UTI in the situations listed in Table 13-5. Whereas urinary tract prophylaxis has been widely accepted, randomized clinical trials comparing prophylaxis to surveillance regimens have not been performed.[261-263] In a recent multicenter, randomized controlled trial, antimicrobial prophylaxis did not decrease the risk of recurrent UTI or the development of renal scarring in children with low-grade reflux (grades I to III) compared with controls.[264] However, for children with high-grade reflux (grades IV and V), retrospective data have shown that reflux nephropathy is less likely in children with high-grade VUR who present without UTI.[265] Currently, there are inadequate data to definitively support the use of antimicrobial prophylaxis, and further investigation is warranted.[266]

Although a number of agents may be used for treatment of a UTI, fewer agents have been studied for low-dose prophylaxis in children. The ideal prophylactic agent should have low serum levels, high urinary levels, and minimal effect on the normal fecal flora; should be well tolerated orally; and should be inexpensive. The potency of these antimicrobial agents is based on the general susceptibility of most fecal Enterobacteriaceae to these agents at urinary levels. Because these agents are generally concentrated in the urine, the urinary drug levels should be much higher than the drug levels found simultaneously in serum, gut, or tissue. If gut levels are sufficiently low, antimicrobial resistance patterns in the gut should not develop. This characteristic of the prophylactic antimicrobial agents is most likely dose-related, so that inappropriately high dosing for prophylaxis may be ineffective because bacterial resistance will be created.[267]

Table 13-6 Oral Antimicrobial Agents Useful for Pediatric Urinary Tract Prophylaxis

Drug	Age Limitations
Useful and Tested	
Nitrofurantoin	>1 mo
Trimethoprim-sulfamethoxazole	>2 mo
Cephalexin	None
Possibly Useful	
Amoxicillin	None
Sulfisoxazole	>2 mo
Trimethoprim	>2 mo*

*Data are limited for this agent.

Because urinary prophylaxis is usually initiated after treatment of an infection for which long-term (7 to 10 days) therapeutic dosing was given, the fecal flora may already be resistant to the treating drug and many of the prophylactic agents, creating a risk for re-infection. This accounts for frustrating "breakthrough" infections that occur soon after the child begins taking prophylactic antimicrobial agents or after treatment of other common infections such as otitis media. The period of greatest risk for recurrent infection is usually the first few weeks after any full-dose treatment. For this reason, the prophylactic agent should not necessarily be the treating agent.

Once urinary tract antimicrobial prophylaxis is initiated, the drug is usually administered until the urinary tract abnormality for which prophylaxis is being given has resolved (e.g., spontaneous or surgical resolution of VUR or obstruction). If resolution does not occur within a few months to years, the time for stopping prophylaxis is unclear. Some evidence exists that renal scarring in girls with pyelonephritis may be less likely after 5 to 6 years of age and may occur less frequently until age 15 to 16 years.[268] Consequently, it may be reasonable to perform a trial of discontinuing prophylaxis when a patient reaches age 5 to 8 years or older if there is no history of UTI and no renal scarring. Although select groups of children have been monitored for years after discontinuing prophylaxis and usually have done well without evidence of UTIs or new scars, these studies have been limited by lack of randomization, radiologic screening technique, and the small number of subjects studied.[263,269,270]

The long-term effects of prophylactic agents on the child and his or her microbial ecology have not fully been examined. A literature review of nitrofurantoin and trimethoprim-sulfamethoxazole prophylaxis in children supported the long-term safety of these agents.[271] More recently, some data have suggested an association between long-term use of antibiotics and increased risk for breast cancer in the adult population. The results from multiple studies in the adult population have been inconclusive and controversial; therefore, further investigation is warranted.[272,273]

In children with normal urinary function, useful agents for urinary prophylaxis that have been studied are nitrofurantoin, cephalexin, and trimethoprim-sulfamethoxazole.[274] Amoxicillin, sulfisoxazole, and trimethoprim alone may also be useful as urinary tract prophylactic antimicrobial agents, but they have not been as well studied in children. In the continent child, urinary tract prophylactic antimicrobial drugs should be given once nightly, so they will be excreted into and remain in the urine overnight (Table 13-6).

Nitrofurantoin is an effective urinary prophylactic agent because its serum levels are low, its urinary levels are high, and it produces minimal effect on the fecal flora.[275] Its effectiveness is based on urinary excretion of antimicrobial once a day, and it has been found to be effective in girls at doses of 1.2 to 2.4 mg/kg each evening.[276,277] If the renal function is reduced to less than half normal, the efficacy of nitrofurantoin may be reduced. Although the majority of nitrofurantoin drug reactions have occurred in adults, it has caused acute allergic pneumonitis, neuropathy, and liver damage.[276] Long-term treatment has been associated with rare cases of pulmonary fibrosis. It should not be used in children with glucose-6-phosphate dehydrogenase deficiencies, because it is an oxidizing agent and can cause hemolysis. About 10% of blacks in the United States, Sardinians, non-Ashkenazi Jews, Greeks, Eti-Turks, and Thais have a glucose-6-phosphate deficiency.

Cephalexin has been studied in adults as a prophylactic agent.[267] Although fecal Enterobacteriaceae resistance has developed in many patients taking full-dose cephalexin (500 mg four times daily), patients taking low doses (one-quarter to one-eighth the adult daily dose: 125 to 250 mg/day) do not appear to develop resistance. Cephalexin at one quarter or less of the treatment dose per weight may then be a useful pediatric prophylactic agent.

Trimethoprim-sulfamethoxazole has proved to be a successful combination drug in the treatment of UTIs and is useful for prophylaxis at a daily dose of approximately 2 mg/kg of trimethoprim.[278,279] Trimethoprim has the unusual characteristic that it diffuses into the vaginal fluid and therefore decreases vaginal bacterial colonization in the female.[280] Because trimethoprim-sulfamethoxazole contains a sulfonamide, it probably should not be used during the first few months of life, because sulfonamides can compete for bilirubin-binding sites on albumin and cause neonatal hyperbilirubinemia and kernicterus. A significant increase in bacterial resistance has been observed to this drug over the past decade.[281]

TREATMENT OF RECURRENT URINARY INFECTIONS

UTIs will recur in most girls, regardless of whether the urinary tract is normal, because host uroepithelial characteristics are an independent risk factor for infection.[130] Current testing does not routinely allow one to predict which patients have a biologic predisposition for UTIs. Routine bacterial biotyping and sensitivity data obtained from culture does not necessarily provide data relating to bacterial virulence. For this reason, management of recurrences depends on the child's age and the severity of symptoms. If the child gets frequent, recurrent infections (two or more over a 6-month period), one may consider urinary prophylactic antimicrobial treatment over a limited period, because the child's biologic predisposition for infections has been established. Antimicrobial agents taken at a prophylactic dosage are usually successful in decreasing the rate of infections during the period of prophylaxis. When the antimicrobial agent is stopped, there may be an extended period of remission from infection, but often the child eventually returns to an increased basic susceptibility for urinary infections.[12,282]

OTHER GENITOURINARY TRACT INFECTIONS

Acute Hemorrhagic Cystitis

Acute hemorrhagic cystitis (AHC) is usually a benign, self-limited disorder in healthy children. Adenovirus is the most common cause of viral AHC in children,[283-285] with *E. coli* occasionally involved. In a series of 69 infants and children with AHC, adenovirus 11 was recovered from the urine in 10 (14.5%), adenovirus 21 in 2 (2.9%), and *E. coli* in 12 (17.4%). However, the remainder (>60%) had no known infectious agents isolated from the urine.[286] Conversely, children presenting with acute adenovirus respiratory infections may develop incidental microscopic or gross hematuria.[287] In healthy children, no antiviral therapy is indicated, because the infection is self-limited. However, radiologic evaluation should be considered to rule out other causes of hematuria.

More recently, AHC has been observed with increasing frequency in children undergoing bone marrow transplantation (BMT). The U.S. National Institutes of Health group reported a 20% incidence in 56 patients undergoing human leukocyte antigen (HLA)-identical sibling BMT, and early development of AHC was associated with a reduction in survival.[288] AHC can be divided into pre-engraftment and post-engraftment subtypes, each with unique etiologies.[289] The pre-engraftment AHC is a result of agents known to be urinary tract toxins, such as cyclophosphamide used to condition the recipient before BMT. Hydration and use of 2-mercaptoethan sulfonate (MESNA) may prevent this type of AHC.

The post-engraftment subtype is more common, occurs 2 weeks to 4 months after BMT, and can be life-threatening. BK virus, a ubiquitous DNA virus of the polyomavirus genus, has increasingly been implicated as the causative agent for AHC in this population.[290-292] Whereas asymptomatic BK virus infection is present in more than 50% of children younger than 10 years of age, the BMT host allows the BK virus to replicate unchecked in the urothelium. After engraftment, the host immune response reacts to the virus in the urothelium, resulting in mucosal injury and hemorrhage.[293,294] Preliminary studies have shown that fluoroquinolones decrease the urinary concentrations of the BK virus when used in a prophylactic fashion, via inhibition of DNA gyrase.[295] However, larger studies demonstrating prevention of AHC are needed.

Treatment of AHC in these children is primarily supportive, because no standardized drug regimen has been developed. Mild cases may be treated with aggressive hydration. More severe cases may require continuous bladder irrigation and fulguration.[296] Immunocompromised children are also at risk for adenovirus-associated hemorrhagic cystitis, and intravenous ribavarin has anecdotally been used to treat such an infection.[297] Cidofovir, a purine analogue, was used in series of BMT patients with some success, but use is limited by nephrotoxicity of the agent.[298]

Epididymitis, Epididymo-orchitis, and Orchitis

Epididymitis is an important clinical syndrome because of its differential diagnosis and management. Epididymitis is often difficult to distinguish from other pediatric acute scrotal processes, especially testicular torsion.[299-301] Although there is some overlap, pediatric epididymitis displays a bimodal age distribution, occurring in very young boys and again in greater numbers postpubertally.[300,302-305] Risk factors include a history of urethral manipulation, recent urinary tract surgery (hypospadias, ureteral reimplantation), catheterization, neurogenic bladder, imperforate anus, and known lower tract genitourinary anatomic abnormalities (ureteral or vasal ectopia, bladder exstrophy).[85,300,306-309]

The symptoms and signs of epididymitis often cannot be clearly distinguished from other causes of the acute scrotum. Characteristics that may be unique to epididymitis include a history of a more gradual onset, dysuria, and urethral discharge. When examined, the scrotum in usually inflamed and swollen; there may be localized epididymal pain; 18% to 33% of affected boys have fever,[300,302,303,306,310] 24% to 73% have pyuria,[300,302,306,310] and 17% to 73% have a peripheral leukocytosis.[300,302,303,310,311] Scrotal color flow Doppler ultrasound and radionuclide testes scans may help to confirm or monitor epididymitis.[301,312-315] Ultrasonography may show an enlarged epididymis of mixed echogenicity surrounded by reactive fluid. Color flow Doppler sonography usually shows increased testicular flow, except when there is such extensive swelling that ischemia may occur.

In young boys and infants, epididymitis is more likely to be related to genitourinary abnormalities or hematogenous dissemination than in older boys.[316] Urethral and urinary cultures from the prepubertal male are likely to show either nothing or gram-negative organisms; therefore, this condition may be referred to as “nonspecific epididymitis.” In postpubertal sexually active boys, the cause may involve sexually transmitted organisms (e.g., *Neisseria gonorrhoeae, Chlamydia trachomatis*). Hematogenous spread to the epididymis is supported by studies in which *Haemophilus influenzae* type b have been cultured from epididymal abscesses, concurrent with other sites of infection such as otitis media, while the urinalysis remains normal.[317-319]

Epididymitis should be treated according to the likelihood of the causative organism. In the young child who has pyuria and possible bacterial epididymitis, initial broad-spectrum antimicrobial treatment similar to that used to treat a UTI in an ill child should be used. Once the culture results and antimicrobial sensitivities are available, the most specific agent that achieves adequate tissue penetration should be administered. During or after treatment of the acute urinary and epididymal infection, radiologic evaluation of the urinary tract should be performed, as with any UTI. Two studies have reported a high likelihood of genitourinary anatomic abnormalities in children with bacterial epididymitis and a UTI—in particular, abnormal connections between the urinary tract and the bowel or genital duct system.[306,320] Finally, when evaluating a scrotal mass, tuberculous epididymitis must be considered, because it is the most common form of urogenital tuberculosis.[321]

Fungal Urinary Tract Infections

As the incidence of fungal UTIs continues to increase, prevention, recognition of risk factors, and diagnosis are critical. The National Nosocomial Infection Surveillance noted a five-fold increase in bloodstream infections. Fungal infections comprised approximately 7% of these infections.[322] In a retrospective analysis of mortality rates from 1980 to 1997, invasive mycotic infections were found to be the seventh leading cause of infectious disease–related deaths in the United States.[323] Candidemia in one neonatal intensive care unit increased more than 11-fold between 1985 and 1995, with a mortality rate of 14%.[324] The urinary tract acts as both a portal for fungal infections and a site of disseminated disease. *Candida* was found in urine cultures in 58% of patients prior to candidemia,[325] and it may serve as the source of blood infection in almost one quarter of the cases. In disseminated disease, the kidney is the second most common site of infection after the lung.

Microbiology and Risk Factors

The *Candida* species are by far the most common cause of fungal UTI with *Candida albicans* accounting for approximately one half of these infections.[326] Other species include *Candida tropicalis, Candida krusei,* and *Candida parapsilosis.* Recent reports have described a marked increase in *C. parapsilosis* systemic infections in children at single centers.[327,328] *C. parapsilosis* tends to proliferate in glucose-containing solutions used in parenteral nutrition formulas, which are commonly prescribed to low-birth-weight neonates; fortunately, this *Candida* species exhibits less virulent, invasive behavior and is associated with lower mortality rates than some of the others.[324,327] The classification of *Torulopsis glabrata,* also known as *Candida glabrata,* remains controversial. Whereas clinical manifestations of *T. glabrata* infection are similar to those of the other *Candida* species, recognition of this organism is important, because it is not nearly as susceptible to the triazole agents. Other causative organisms of fungal UTI include *Aspergillus, Cryptococcus,* and *Coccidioides.* Although these organisms were rare in the past, they are seen with increasing frequency in patients with acquired immunodeficiency syndrome (AIDS) and in those undergoing transplantation.

Contributing factors in fungal UTI have been well delineated. As described by Keller and colleagues, predisposing factors for genitourinary candidiasis in neonates include antibiotic therapy (57%), prematurity (29%), intravenous catheters (24%), and parenteral alimentation (18%).[329] Candidal UTIs are unique in that they may occur via hematogenous dissemination or by retrograde ascent. Finally, immunosuppression, either iatrogenic or disease related, has emerged as a major risk factor for genitourinary fungal infections.

Candidal Lower Urinary Tract Infections

Candidal infections of the lower urinary tract are most often associated with the presence of an indwelling urethral catheter and long-term therapy with antibiotics. Lower urinary tract obstruction may play a role. Hitchcock and coworkers described two cases of candidal bladder infections in patients with posterior urethral valves[330]; both patients had placement of suprapubic catheters that subsequently became infected. Infections resolved after valve ablation, appropriate drug therapy, and catheter removal.

Deciding which lower urinary tract candidal infections to treat is both challenging and controversial. Patients with indwelling urinary catheters may be colonized and yet rarely develop systemic infection.[331] Little controversy exists, however, regarding the need for treatment of symptomatic patients, patients undergoing urinary tract surgery or manipulation, immunocompromised hosts, and premature, low-birth-weight infants. The last group, in particular, should be aggressively managed, because urinary candiduria is a reliable marker of disseminated infection. Diagnosis can be made by urine culture, although the colony count that defines significant candiduria remains controversial. Wise and colleagues recommended treating when repeat cultures demonstrate greater than 10,000 CFU/mL.[326] As with bacterial specimens, it is critical to obtain the urine specimen properly. Fungus-specific urine cultures may be necessary in certain institutions to obtain speciation and colony counts, because these factors may alter therapy.

Treatment of localized bladder infection begins with changing and, if possible, removing urinary catheters and discontinuing unnecessary antibacterial agents. Amphotericin bladder irrigation has been widely used in the treatment of candidal cystitis[332,333]; however, dosage, length of treatment, and method of delivery have varied considerably. Controversy exists as to whether intermittent versus continuous irrigation with amphotericin B is most effective.[334] Accepted irrigation regimens use amphotericin B at a concentration of 50 mg per liter of irrigant infused at 42 mL/hr for 24 to 48 hours. More recently, adult patients have been treated with oral fluconazole, and results have been equivalent to those achieved by amphotericin irrigation, with a more benign side-effect profile.[335] Case reports describe the use of fluconazole to treat fungal bladder infections in children (see later discussion).

Candidal Infections of the Kidney

The kidney is a common site of end-organ disease in disseminated candidiasis, with a variety of clinical manifestations including abscess (solitary or multiple), pyelonephritis, and fungal bezoar in the renal pelvis causing obstruction. In infants and adults with disseminated candidiasis, the kidney was found to be the organ most commonly harboring disease.[329] Hurley and Winner, using a mouse model, described two patterns of disseminated candidal infection.[336] Large doses of the *Candida* led to multisystem disease with a poor prognosis. Smaller doses, however, created low-grade disease in organs such as the kidney, where chronic renal atrophy and fungal ball formation were observed.

Diagnosis is based on blood and urine culture, yet 24% of infants with multiple renal fungal abscesses have a negative urine culture. Ultrasonography is essential to rule out a fungal bezoar in the renal pelvis that could result in obstruction; anuria secondary to bilateral fungus balls has been reported in neonates.[329,337,338] In fact, an ultrasound study should be performed if disseminated candidal infection is suspected in a neonate. Other tests, such as IVU and nuclear scintigraphy, rarely assist in making the diagnosis.

If a fungus ball is present, percutaneous nephrostomy is recommended.[337,339] Percutaneous nephrostomy definitively relieves obstruction and prevents ongoing parenchymal insult, provides a "clean" specimen and an accurate diagnosis of the fungal infection, and allows treatment of the infection with local instillation therapy complementing systemic therapy.[340] Amphotericin B is the agent most commonly used for instillation therapy, given its efficacy against most fungal species. The duration of therapy is poorly defined but ranges from 6 to 14 days, depending on resolution of the filling defect in the renal pelvis and negative blood and urine cultures. Both continuous and intermittent dosing regimens have been described, but amphotericin concentrations in the irrigant have not been standardized. Persistence of fungus balls despite percutaneous nephrostomy, local instillation therapy, and systemic therapy has been reported.[341] In such cases, surgical removal of the bezoar is indicated.

Systemic therapy must complement local instillation therapy. Amphotericin B remains the gold standard in treating disseminated or life-threatening candidal infections, but the associated toxicity requires close monitoring of renal function and hemodynamics. Nephrotoxicity can be minimized with adequate hydration, limiting the use of other nephrotoxic agents such as intravenous contrast and aminoglycosides.

Fluconazole, an azole that inhibits fungal cell wall synthesis and has been available for more than 15 years, has been used successfully to treat systemic candidal infections in both neonates and children, although it is not approved by the U.S. Food and Drug Administration for use in infants younger than 6 months of age.[342-344] Fluconazole offers several therapeutic advantages compared with amphotericin B, including excellent tissue penetration, low fungal resistance rates, high urinary concentrations, and lower toxicity.

Fluconazole has been used successfully as prophylaxis for preventing invasive candidal infections in very-low-birth-weight infants (<1000 to 1500 g), and in some reports it has reduced the mortality rate.[345,346] Despite its increased use in all populations over the last 15 years, most fungal species remain susceptible to fluconazole, making it a first-line agent for candidal infections.[347]

Pediatric Interstitial Cystitis

Interstitial cystitis is a poorly understood symptom complex that may include pain with bladder filling, pelvic pain, urinary urgency, urinary frequency, and nocturia. Hunner first described this entity in 1915, in patients presenting with fibrotic, shrunken bladders and ulcerations.[348] Stamey and Messing refined the definition of interstitial cystitis based on a symptom complex and the presence of glomerulations after hydrodistention of the bladder.[349] Despite numerous theories, the etiology of this disease has not yet been clearly defined.

Interstitial cystitis remains a controversial diagnosis in children. Indeed, a variety of other self-limited dysfunctional voiding syndromes can mimic some of the symptoms of interstitial cystitis. Zoubek and colleagues reported spontaneous resolution of symptoms in patients with extreme urinary frequency and otherwise normal examinations and studies.[350] Hanno and coworkers cautioned that diagnosis in childhood is "extremely rare" and should be differentiated from urinary frequency syndromes.[351] Although interstitial cystitis remains a diagnosis of exclusion, a genetic predisposition may exist. Adult first-degree relatives of patients with interstitial cystitis have an increased prevalence 17 times that of the general population, with implications for children and adolescents unknown.[352] As with adults, no standardized treatment regimen has been proposed. Hydrodistention was noted to be effective in some patients.[32] Current therapy in adults including oral agents such as Elavil (amitriptyline) and hydroxyzine and local therapy with dimethyl sulfoxide (DMSO), heparin, or Clorpactin are options, but, given the rarity of interstitial cystitis in children, none of these options has been evaluated for efficacy or safety.

Other Urinary Tract Infections

There are several important infectious agents with multiple manifestations in the urinary tract that are beyond the scope of this chapter. Urinary schistosomiasis from *Schistosoma haematobium* infection affects 80 to 90 million people worldwide, with the preponderance of cases in developing nations. *S. haematobium* infection is particularly important in children, in whom the early active stage may manifest as gross hematuria, terminal dysuria, and frequency. Others have provided comprehensive reviews of schistosomiasis in childhood[353] and infection of the urinary tract.[354]

Urinary tuberculosis can affect almost any portion of the genitourinary tract. However, because of the latency period after primary infection, disease in children is relatively rare. Gow has written a comprehensive review of genitourinary tuberculosis.[355]

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CHAPTER 14

NURSING INTERVENTION IN PEDIATRIC UROLOGY

Caroline Sanders

The role of the nurse caring for infants, children, and young people in urology includes the following:

- Education and preparation: possibly antenatal, preadmission, at admission, during the hospital experience, and after discharge
- Communication: with children and their families and among professionals
- Support and counseling
- Clinical skill in the coordination, delivery, and management of care

Pediatric urologic surgery is often planned, allowing parents and nurses the opportunity to have an active role in preparing children for surgery. Hospital and surgical interventions can create real or imagined fears for children, so it is important to prepare children for surgery.[1,2] Hospital attendance and surgical intervention and investigations can also cause parents anxiety.[3] Parents need to be reassured that they will be able to accompany their child throughout their stay, including during investigations and into the anesthetic and recovery room. Anticipatory anxiety about a hospital admission can be influenced by factors such as previous hospital experience and the child's developmental level.[4] Children with chronic and complex urologic issues, such as bladder exstrophy, may have different worries from those experiencing their first or perhaps their only admission for surgery.

GENERAL PREPARATION AND EDUCATION

With the exception of infants, all children need advance preparation for elective procedures.[5,6] Open communication among children, parents, and health care professionals explores concepts of trust[7] and facilitates the sharing of information and development of understanding and knowledge, which are important concepts within the process of "informed consent."[8] The nurse should ensure that the child and the parents have an understanding of the urologic condition, the treatment, outcome, and follow-up care.

Preoperative visits and assessments that consider the child's developmental level and understanding can allay fears, correct misconceptions, and help foster a positive experience.[6] Traditional preparation methods of communication that aim to increase knowledge and understanding include therapeutic play, expressive play with dolls and puppets, videos, and written literature. Children often find it difficult to conceptualize their internal anatomy, and simple pictures and diagrams can help facilitate understanding. Multimedia approaches and the Internet are new tools that can be effectively used by parents and practitioners when preparing children for admission and surgery.[9,10] Children and their parents sometimes feel isolated, as if they were "the only ones experiencing this problem,"[10] and visiting other children who have similar birth conditions or experience of surgery can help. Independent advice can be sought from self-help groups.

The timing of sharing information is based on the child's stage of development, complemented by parental guidance and advice. Information given too early to an acutely anxious child may heighten worry and increase anxiety and fear. On the other hand, withholding information can cause the child to arrive at the hospital without being prepared for admission, resulting in loss of trust in caregivers. Children who are admitted on an emergency basis will have had little time for preparation and are often unwell and in acute discomfort. The child's immediate concern often relates to stopping their pain; once this is controlled, the child and parents will need information and preparation for any interventions that may be necessary.

Infants

Primarily, the information provided in the case of a infant should be focused toward the parents or caregivers. Parents may have concerns about the practicalities of the elective admission, such as sleeping at the hospital, staying with their child, and visiting. Parents are often involved in the care of their children during admission, and this may need to be acknowledged or negotiated.[11] Developmentally, infants have a secure relationship with a parent or caregiver, and separation can have an emotional impact on the child.[12] Whenever possible, urologic procedures (e.g., orchidopexy) should be managed in the outpatient or day care surgery setting, to minimize both the length of stay in the hospital and the changes to routine.

Preschool Children

Children in the preschool-age group (1 to 4 years) are becoming more aware of their surroundings and beginning to explore. Some children may view admission to the hospital as a punishment and may experience regressive behavior or anxiety as a result of separation from their parent. Familiarizing the environment with toys and smells (e.g., blankets from home) may help to settle a child. Hypospadias surgery is often carried out at this age, to limit any possible future psychological or psychosexual effects of genital surgery.[13] Educating parents about possible changes in their child's behavior after an admission maybe helpful.[14] Parents may notice that their child is more "clingy" after a hospital admission, and there may be disruptions to normal routines, such as sleeping. This behavior is often self-limited, and parents may benefit from accessing their local community services, such as a health visitor in the United Kingdom, for ongoing support.

School-Age Children

Children in the school-age group (5 to 11 years) are becoming more autonomous and questioning about their health and reasons for surgery. The goal of the nurse is to gain the trust of the child and family, giving them the opportunity to question in a nonjudgmental and empathic atmosphere. Education and checking out the child's understanding are important.

For example, if the child will require catheterization (CIC) after surgery, then CIC will need to be in place preoperatively. Trying to teach children new skills after they have experienced surgery can be problematic and can cause difficulties later with concordance.[15] Encouraging children to develop a positive view about their bodies and urologic or continence needs can help with future independence and self-esteem. Children who can develop confidence and trust in the nurse may feel more secure when discussing sensitive issues.

Adolescents

Young people should be involved in making decisions about their health and surgical procedures.[8] Preoperative preparation for adolescents can be especially difficult if they wish to discuss sensitive issues. The adolescent should be offered the opportunity to explore concerns without their parents' being present (if they wish). A variety of media can be used to manage this situation, including a journal or e-mail (if the local organization considers this appropriate or policies are in place to safeguard both the child and the professional). Confidentiality and privacy should be maintained and support given to the parents, because they may be reluctant to relinquish control about decisions and often feel very protective toward their child.[8] For example, discussions about sexual activity, risky behaviors, genital sensation, fertility, and body image are topics that are highly sensitive yet need to be considered with the young person. Ongoing psychological support may be of benefit, and the nurse should be able to refer the adolescent to the most appropriate health care professional.

Adolescence is a time of change and growth for both the child and the child's relationship with the parents.[16] Changes can include physical and psychological growth, experimentation, sexual exploration, changes in behavior, school life, and mental health needs (including easting disorders, self-harming behavior, body image issues).

Additional pressure, such as a chronic urologic condition or difficulty with continence, can further impact the adolescent. Often adolescents challenge their health needs, resulting in a lack of adherence to bladder management routines. The nurse needs to be able to continue to support the adolescent, listen, and help manage parent/adolescent disagreements relating to health issues.

Children with Special Needs

Children with special needs may have additional health requirements outside of their developmental needs. Discussion with parents several weeks before elective surgery can facilitate an easier admission. Equipment from home may need to be brought to the hospital, such as a wheelchair or special feeding equipment. Children with autism may benefit from preadmission visits, so that they can develop a coming-to-hospital routine or booklet specific to them, making attendance on the day of surgery less traumatic.

SPECIFIC UROLOGIC ANOMALIES

Hypospadias

Hypospadias, a developmental malformation, is described in Chapter 41. Surgery related to hypospadias is commonplace in urology clinics.[13] When parents first learn about their son's hypospadias, they are often anxious about the appearance of their son's genitalia and the future outcome for him. Parents may not discuss the subject of their son's genitalia with family or friends, because it can still be regarded as a sensitive or taboo subject area. Parents may therefore rely on support and advice from nursing and medical staff or self-help groups (e.g., see http://www.hypospadias.co.uk [accessed January 2009]). Ideally, infants with hypospadias should be referred to a pediatric urologist/surgeon as soon as possible. Although surgery is not undertaken before the age of 1 year, early consultation with a surgeon can help to allay parental concerns. More importantly, early referral of a child with severe hypospadias (or genital ambiguity) and cryptorchidism is advocated, because these children may have a disorder of sexual differentiation.

Preoperative Information (in the Clinic)

At the first consultation, the surgeon will reassure parents about the long-term outcomes from surgery and that the repair will not change their son's chances for fertility and potency. Although there are many approaches for correcting hypospadias all aim to achieve

1. A meatus at the tip of the glans and a straight penis
2. The ability to void easily in the standing position
3. A good cosmetic outcome

The surgeon will provide an overview of the surgery and treatment and decide whether the child will benefit from preoperative treatment with testosterone. If necessary, this hormone will be administered either topically or intramuscularly, but it will not be started until a date for surgery has been scheduled. If the topical route is chosen, advice on reapplication and treatment duration is given to the parents. Parents should remember to use a glove to apply the cream or ointment, to minimize their exposure to the hormone, and also to observe for side effects, which include sore skin, change in temperament, and sparse pubic hair growth. Testosterone injections are given intramuscularly at 3-weekly intervals for up to three doses before surgery. The hormones increase the blood supply to the genitalia, causing enlargement of the penis; parents need to be aware of the expected outcome from treatment.

The nursing preoperative care varies according to region or country and can range from nurse-led preoperative clinics to telephone contact.[17] Through these, the child can be assessed for fitness for surgery. Specific questions about diaper rash should be asked, because the surgery should be rescheduled if the child has an infected genital area. The urology nurse should be able to answer any questions related to the surgery, outcome, and hospital routine.

Postoperative Care

Most hypospadias surgery procedures in the United States are performed on an outpatient basis; in the United Kingdom, some hypospadias surgeries may necessitate an overnight stay. Because of the short length of stay and parents' anxiety, it is very important that parents receive appropriate and precise written information about caring for their son at home after surgery. Written information should consider the aspects covered in the following paragraphs.

SURGICAL SITE AND DRESSING

Absorbable sutures are used for the repair; only a stay suture securing any stent (if used) will need to be removed. Over the last 20 years, various dressings have been used[17]; however, the surgeon's discretion determines the dressing type, duration, and removal approach. Many centers opt for clear dressings such as Op-site or Tegaderm, whereas others may use foam dressings such as Cavicare (Fig. 14-1). Some centers do not advocate the use of a dressing postoperatively.[18,19]

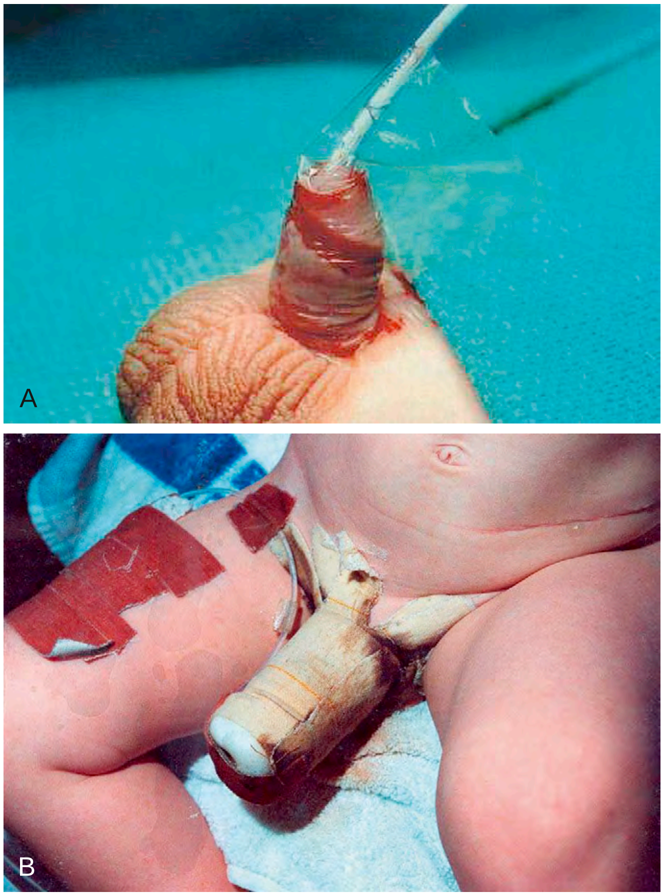

Figure 14-1 Two examples of hypospadias dressings. **A,** Translucent dressing. **B,** Foam dressing. This dressing was soaked in the bath just before removal, after being in place for 1 week. (Photograph in **A** courtesy of W. Snodgrass.)

It is not uncommon for a small amount of blood to ooze under a clear dressing or through foam dressing. Parents should be aware that this could happen and under what circumstances to call back for advice.

If the dressing becomes soiled with stool, parents can be instructed on how to clean the area; if a nonocclusive dressing is used and the foam dressing becomes heavily soiled, parents should call for further advice. Some surgeons request that the dressing not be soaked in the bath for the first week after surgery, whereas others advise immersing the child in a warm bath for 3 to 5 minutes several times a day, starting on the second postoperative day. Bubbles and soap may cause skin irritation and should be avoided. Those surgeons who allow early baths may also recommend that the dressing be soaked off while the child is in the bath (which is possible if there is no stay suture or stent in place).

Parental concerns about the hypospadias dressing prompt many postoperative calls to the urology nurse, team, or ward where the child was treated.

Drainage

Some surgeons use a urethral stent postoperatively to minimize the chance of urine coming into contact with the neourethra and to support the surgical site during the healing process.[13] Other surgeons use a stent but drain the bladder via a suprapubic catheter. Any type of stent or drainage tube can cause parental anxiety, especially if the parents must care for it at home.

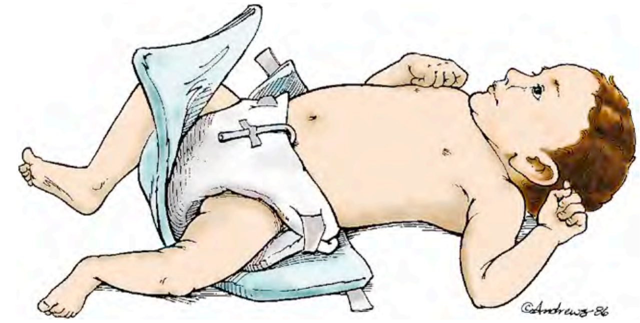

Figure 14-2 Double-diapering method for management of urine drainage after hypospadias surgery. (From Montagnino BA, Gonzales ET Jr, Roth DR. Open catheter drainage after urethral surgery. *J Urol.* 1988;140[5 Pt 2]:1250-1252.)

Parents may become anxious about the stent's falling out or becoming dislodged. In some cases, the stent is attached to the glans with a nonabsorbable suture. This suture and dressing usually prevent the stent from becoming dislodged. If the stent were to fall out unexpectedly, parents should be told to call for advice and not to try to replace the stent.

The stent can be managed by the use of a double-diaper (Fig. 14-2). This technique requires application of two diapers in the normal fashion, with the stent being sandwiched between the first and second diaper. The stent is taped to the inner diaper to avoid kinking. This approach can protect the stent and repair while allowing the toddler some mobility. Other centers drain urine via the stent and collect it in a drainage system. Regardless of the system used, parents need to be confident and comfortable with managing their child's care when leaving the hospital.

Initially, the urine draining from the stent may be blood stained, and, occasionally, a piece of mucus or blood clot may be seen. Encouraging the parents to increase their son's fluid intake and making sure the catheter does not become kinked will facilitate good drainage. If the tip of the penis is visible through the dressing, application of a small amount of antibiotic ointment may be recommended by some surgeons to prevent crusting around the stent.

Analgesia

Parents are often surprised when their son experiences very little postoperative pain initially after hypospadias surgery. This is due to the use of caudal analgesia during the surgery, which is often effective for 6 hours postoperatively. Oral analgesia can be given to the child as prescribed, and parents should be cautioned to give only the medication prescribed, and only in the correct dose and frequency.[13]

Bladder Spasms

Bladder spasms occur in children with a urethral stent, and the frequency varies among individual patients. A sudden intense pain that usually passes very quickly, which differentiates it from incisional pain, characterizes bladder spasms. Older children may complain of pain in their penis or rectum. As long as the stent is in place, no medication can completely eliminate the spasms; however, administering a prescribed anticholinergic and carefully monitoring the stent for kinks and for small clots of mucus or blood will make the child more comfortable. Ensure that any drainage device fitted to a stent or catheter is appropriate for the child's size. Empty the drainage before it is too full. Sometimes it is helpful to place the drainage bag on a level with the child, minimizing any excessive pressure in the drainage system.

ANTIBIOTIC

Some surgeons advocate the use of antibiotics until the dressing is removed; these can be given in either a prophylaxis dose or a treatment dose. Limited empiric evidence exists to guide clinical use or effectiveness of antibiotics after repair, either while the dressing is in place or after removal.[20]

DIET

Clear fluids, very dilute juice, or popsicles are encouraged immediately after recovery from anesthesia, building back to a normal diet and fluid intake. Many children have decreased appetite for 2 to 3 days after surgery. This is not a cause for concern, but parents should encourage adequate fluid intake to maintain urine flow. To prevent constipation, offer the child high-fiber foods such as fruits and cereals.

ACTIVITY

Quiet, gentle activity is allowed after surgery, although some centers suggest very little activity after surgery until the dressing is removed. The child should not use any straddle toys or engage in any activity that requires straddling. Clothing can hide the dressing and stent and may discourage the child from handling the repaired penis.

PARENTAL SUPPORT AND MANAGEMENT OF PROBLEMS

During the early postoperative period, parents may worry about the dressing, drainage, and the appearance of the penis if it is visible through the dressing. Advice given before discharge about what to expect over the first few days postoperatively may decrease the number of calls from worried parents. Often, the penis is edematous, and the penis and groin area maybe bruised. Edema and bruising will settle as healing takes place over the next few weeks after surgery.

Before the child's discharge, written instructions regarding when to recontact the hospital are given to parents. The nurse should check that the family has understood that the hospital should be contacted in the following situations:

- The child vomits more than three times and is unable to tolerate clear fluids.
- Continuous bleeding is noted under or through the dressing.
- The outer diaper is dry and the stent is not draining.
- The foam dressing is very wet.
- The child soils the dressing, and it cannot be adequately cleaned.
- The stent falls out (do not attempt to replace the stent).
- Excessive swelling or discoloration is noted in the penis or scrotum or both.
- The child has a fever of 102° F or higher for longer than 24 hours.
- The child without a stent has difficulty urinating.
- The dressing appears too tight or has slipped to cover only the shaft.
- The child is in severe pain despite taking pain medication as prescribed.

DRESSING REMOVAL

Typically, the dressing stays in place for 3 to 5 days for distal repair, 5 to 7 days for proximal repair, or 7 to 10 days for two-stage repairs or grafts. This is at the surgeon's discretion, and little rigorous evidence exists in the literature to substantiate the most effective duration of dressing.[17]

If the dressing falls off before scheduled removal, some centers suggest that parents apply topical antibiotic ointment to the penile area. Sometimes, when the dressing comes off, the penis swells slightly; parents should be made aware of this possibility and given advice to contact the nurse if the child has any difficulties in voiding. It has also been suggested that application of the ointment may stop the penis from adhering to the diaper.

Removal of the dressing ultimately depends on the type of dressing used. The urology nurse should be knowledgeable about those techniques used in his or her own clinical area. Once the dressing has been removed, some centers advocate the use of antibiotic ointment to the repaired area or urethrally. Once the stent has been removed, parents are asked to stop administering the anticholinergic medication. Swimming is allowed after 2 weeks. Older children may resume contact sports after 6 weeks.

Complications

The incidence of complications after hypospadias surgery varies and is reported in the literature.[21] Complication rates vary depending on the severity of the hypospadias, the surgical approach used, and the experience of the surgeon.

POSTOPERATIVE AND SHORT-TERM COMPLICATIONS

Wound Infection. For bacterial or fungal infection, some surgical teams advocate the use of prophylactic antibiotics while the dressing and catheter are in place and topical treatments once the dressing is removed. Oral antibiotics may be necessary, and the wound can be swabbed to identify the infective organism.

Hematoma or Edema. Although hematoma may appear unsightly, often no further treatment is necessary, unless it is of a significant size and could interfere with wound healing. If the foreskin was reconstructed, edema could restrict voiding, and it is important to check that the child is passing urine well once the dressing and stent are removed. If the child is unable to void after the dressing and stent have been removed, he will need medical review and possibly insertion of a suprapubic catheter.

Dysuria. Voiding after removal of the dressing and stent can be painful in boys who are more aware of their hypospadias surgery (>2 years of age) and in those that are toilet trained. Regular analgesia may be required, and the child may need to be placed in a warm bath to encourage him to void until he is more comfortable. Dysuria can also be a transient problem when the remaining sutures dissolve and are passed, sometimes several weeks after surgery.

Urinary Tract Infection. Very rarely, boys may develop a urinary tract infection after hypospadias surgery.

Urethral Fistula. This is a fine channel between the neourethra and the penile skin; it can appear anywhere along the repair, and there can be more than one fistula. Often, the fistula is identified when the child or his parents notice two or more streams during voiding, which may not be until toilet training is started. Surgery to correct the fistula is not usually undertaken until the repair has had sufficient time to heal, at least 6 months after the primary repair.

LONG-TERM COMPLICATIONS

Meatal Stenosis. This is a narrowing of the urethra at the glans penis. The urethral opening looks very small and may be described by parents as having a "pinhole" opening. Often, parents report that their son has a fine urinary stream, but some may report that their son takes a long time to void. A uroflow study can be helpful to identify an obstructive flow rate. For some boys, treatment can be daily urethral dilatation with an appropriately sized, lubricated catheter. Treatment often continues until the stream has improved and is often referred to a stricture therapy.[22] Alternatively, the neourethra may need to be dilated under general anesthesia, or further surgery may be indicated.

Urethral Diverticulum. This occurs when the child's urethra balloons as he voids. Urine collects in the areas of the dilated urethra, sometimes resulting in the child's wetting, after he has been to the toilet, as the pooled urine is able to dribble out. The child can express his urethra after micturition to minimize any dribbling.

Urethral Stricture. This may develop over time and may manifest several years after surgery. As with meatal stenosis, the stream is fine and the child takes an increased length of time to void. However, the urethral opening often looks to be of a good size, and this helps the nurse distinguish between meatal and urethral stenosis. Because of the nature of the stricture causing an obstruction, the child may develop residual urine in his bladder, urinary retention, urinary tract infection, or dysfunctional voiding.

Residual Chordee. This is often noted when the child reports his penis being bent or painful when he experiences an erection. Further surgery may be necessary to correct chordee, preferably before puberty.

Vesicoureteral Reflux

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder into the upper tracts of the urinary system. Its causes and treatments are covered in detail in other chapters. The nurse has several roles in caring for children with VUR, which can include

- Diagnostic investigations
- Education (of parents and child)
- Monitoring of treatments, including early urine testing and management of breakthrough infection
- Bladder training or biofeedback in those children with low-grade VUR and dysfunctional voiding or overactive bladder
- Care of the child who needs surgical intervention to correct VUR (STING operation or reimplantation of ureter)

Investigations

Although diagnostic investigations are often undertaken in the ultrasound, x-ray, or nuclear medicine departments, some nurses have a role in catheterizing the child for the investigation. The nurse has a role in educating the child and family using the methods previously discussed. In some circumstances, sedation may be necessary, and this should be prescribed and administered according to local policy.

Monitoring of Treatment

Because the goal of medical management for VUR is to prevent any urinary tract infections and subsequent renal damage, parents need to know how to collect a urine sample. The collection of an uncontaminated urine specimen from infants is challenging.[23] Varying techniques are reported in the literature, including clean-catch technique, cotton-wool pads, and urine bags, with clean-catch remaining the gold standard. If a sample has been collected, parents should inform the nurse, so that early effective treatment can be initiated as necessary.

The use of prophylaxis and outcome is well documented in children with VUR.[24] Parents need to be able to administer the medication regularly and should report any side effects or intolerance of the medication to the nurse. The prophylactic agent used depends on local policy and national guidelines. Many parents worry about their child's taking antibiotics regularly and consider prophylaxis a burden. The nurse should offer ongoing support and monitor adherence. If there are concerns that the child is not receiving his medication, alternative treatment options may need to be considered.

Bladder Dysfunction

Some children with VUR experience voiding dysfunction or overactive bladder.[25] Interventions that aim to improve the child's voiding dysfunction can possibly improve outcomes for the child with VUR. A good history from the child and parents can help identify voiding dysfunction; questions should focus on voiding patterns, postures, urge, stream, pain, flow, and continence. A history of bowel habit should also be taken, because constipation can lead to poor bladder emptying. Various approaches may be used to encourage the child to establish a good, relaxed voiding routine, including biofeedback[26] and possibly anticholinergic medications.[27]

Surgical Management of VUR

The indications for surgical treatment of VUR are breakthrough infections while taking antibiotics, progressive renal scarring, persistent high-grade reflux, and anatomic abnormalities at the vesicoureteral junction (VUJ) or anywhere in the genitourinary system, intolerance to the antibiotic, and newly diagnosed reflux in older children. Five to 7 days before any surgery, the child's urine is tested for any indication of infection, and treatment is commenced as necessary.

Endoscopic treatment is used in some centers as a primary approach to treating VUR.[28] This is day surgery or outpatient surgery, and it involves a cystoscopy and injection of a nontoxic, nonmigrating substance into the refluxing ureteric orifice.

Unilateral or bilateral reimplantation of the ureter is performed if endoscopic treatment has failed, was not a treatment of choice, or was considered unsuitable. The surgery can be open or laparoscopic, and there will be a scar. Body image can be important, and parents and children will want to know about the position of the scar and the type of stitches in place, whether there will be any drainage tubes, and when the child can go home. Specific advice that relates to the center undertaking the surgery should be provided; this allows parents to have both verbal and written information preoperatively, enhancing informed decision making.

Postoperatively the child may have ureteric stents in place to ensure drainage of urine past the VUJ. The child may also have a small drain under the incision, which can stay in place for 2 to 7 days depending on the amount of loss. The wound can be covered with a simple dressing and changed daily or more frequently as needed. Depending on age, the child may have an opiate infusion postoperatively to minimize pain. There may be an indwelling urinary catheter postoperatively; this can be removed based on medical advice. Until the child is tolerating fluids and diet, PR analgesia can be used; once the child is eating and drinking, oral analgesia can be offered. The ureteric catheters can cause some children to experience bladder spasms; if this is the case, anticholinergic medication can be started. The nurse needs to be aware of the side effects of this type of medication; constipation should be avoided, because it can cause additional discomfort for the child.

Children are often discharged from the hospital once they have recovered from the surgery and are ambulant and their pain relief is well managed. This often means that they will go home with one or more stents in place. The parents should be advised on how to care for any catheters or stents in place along with general wound care advice. It is advisable to warn parents that the urine will be blood stained and the child may experience a small degree of urinary incontinence, which will resolve once the bladder has healed. Parents should contact the nurse if they have any worries or concerns, but especially if the child experiences any of the following:

- Unmanageable bladder spasms
- No drainage or passing of urine for more than 8 hours
- Pyrexia
- Difficulties taking or tolerating the medication prescribed
- Unmanageable pain
- Wound redness or swelling

The child is reviewed in the clinic 1 week after surgery to check the surgical wound and remove the stents. Analgesia and distraction are used as tools to facilitate the child's comfort while the stents are removed. The child can continue on prophylaxis until the postoperative ultrasound is clear (1 month after surgery) or until the surgical team evaluates the child 4 to 6 months after surgery.

Pelviureteral Junction Obstruction

Obstruction at the PUJ may cause the child to develop hydronephrosis or experience renal pain. Any obstruction (e.g., at the PUJ) in the urinary system may be noted on antenatal scanning as hydronephrosis; such babies should have a follow-up scan 24 to 48 hours after birth. A child with an acute PUJ obstruction can present with symptoms of renal colic, which can be very distressing. In acute obstruction, the child may need a nephrostomy tube to allow the collecting system to drain. This can stay in place for several weeks, and the child and family will need to be taught how to care for the drainage system. If a PUJ obstruction is caused by stone disease, treatment may initially include insertion of a double JJ stent and lithotripsy.

The surgical approach to correct PUJ is a pyeloplasty undertaken by open surgery, laparoscopically, or by pyelolithotomy if there is stone disease. Education and support are given preoperatively, as outlined earlier, and the child will need routine preoperative tests (urea and electrolytes, full blood count, group and save, and urinalysis). Once again, surgical scars should be discussed with the child and family.

The child may return from the operating theater with either a nephrostomy tube and a ureteric stent or a double JJ (internal) stent in place. One end of the double JJ stent sits in the renal collecting system, and the other in the bladder. This can stay in place for 6 weeks to 6 months, depending on the surgery, and it is taken out as an outpatient procedure via a cystoscopy. If the child has a nephrostomy and external stent, the stent often stays in place for approximately 1 week. After this time, the stent is removed and the nephrostomy tube is clamped. If the kidney is able to drain freely, the child remains pain free, and no leakage of urine should be noted from the surgical site. After 24 hours of clamping, the nephrostomy tube is removed.

Parents should contact the nurse if the child experiences problems, as highlighted in the earlier section on VUJ surgery.

Bladder Exstrophy and Epispadias

Bladder exstrophy is a very rare birth defect and requires the skill of a surgeon who regularly undertakes major reconstructive surgery in children. This type of surgery is increasingly undertaken in specialist centers, where the child can have access to pediatric urologists.

This anomaly happens early in embryonic life and results in the child's being born with the bladder exposed. The pelvic bones are separated, and boys have an epispadias, whereas girls have a bifid clitoris, anterior urethral opening, and short vagina, possibly with a septum and anterior anus. It is sometimes possible to detect this anomaly antenatally, but often the birth defect is a surprise for parents and practitioners delivering the baby. The abnormality is clearly visible at birth and causes parents distress. The exposed bladder should be covered with a nonadherent soft plastic (film), and the baby should be transferred to a specialist center able to deal with the anomaly. This can mean a separation for the baby and mother. This is a very anxious time for the family, because these babies often have surgery early in life.

A variety of surgical techniques exist to correct the anomaly, most of which are reported in the literature.[29,30] The nurse should ensure that information is given to the parents and that they have the opportunity to ask questions and time to bond with their baby. Parents' experiences at this time are likely to be significant across their child's life; therefore, sensitivity and confidentiality of any information sharing are imperative.

The aims of surgery include preservation of renal function, attainment of continence, reconstruction of abdominal wall (cosmetically good), and reconstruction of genitalia (maximal penile length in boys and vaginal integrity in girls).

The aims of nursing/psychologists and other professionals include the following:

- Promote a positive body image in the child and facilitate concordance with medical care.
- Empower parents to be able to support their children.
- Provide psychological or psychosexual advice and support/counseling.
- Support the child and family in all areas of life, including continence, sexual health, sexuality, and integration in school life.
- Put the families in contact with self-help groups and independent organizations (access is their choice).
- Prepare young people for transition to adult services.

Surgery

Staged bladder surgery involves initial closure of the bladder (early after birth) and later repair to the epispadias (at 12 to 18 months of age). Some surgeons have advocated combined repair of the exstrophy and epispadias defect as the initial management, closing the bladder and repairing the epispadias in one procedure. Nursing care for either the staged approach or complete primary closure is similar.

Preparation is imperative, as discussed previously. To facilitate bladder closure, the pubic bones must be brought closer together; this is usually done by cracking the pelvic bones (osteotomy) to allow the pubic bones to be moved closer to the anterior midline. If closure is done within the first 24 hours of life, osteotomy may be unnecessary, because the effects of the maternal hormone relaxin allows the newborn's pubic bones to be brought together more easily. Bony healing of the pelvic ring takes 4 to 6 weeks. Immobilization of the pelvis is necessary to promote bone healing and to avoid dehiscence of the newly closed bladder. In the newborn or infant younger than 1 year, usually a spica cast or modified Bryant's (gallows) traction is used to immobilize the pelvis. In older infants and children, the external fixator is often used. If a spica cast is used, a window is cut in the cast for observation of the operative area and to allow diaper changes. When the cast has completely dried, moleskin is placed around the inner surface of the cast to protect the child's skin from the rough cast edges. If an external fixator is used, the nurse can reassure the parents that the pins are not uncomfortable. Before the child is discharged, the parents are taught how to care for the cast or fixator. The fixator is usually removed after 6 weeks.

Usually, three urinary drainage tubes are left in place, a suprapubic catheter to drain the bladder, and two ureteric stents to drain the urine from the kidneys. All the tubes are monitored closely for possible occlusion, and initially these tubes will drain blood-stained urine. The urinary output is measured and recorded regularly, with any significant reduction in the amount of drainage or increasing hematuria reported to the surgeon. Periodic irrigation of the tubes with sterile normal saline solution may be ordered. This is to facilitate drainage or relieve obstruction as necessary; otherwise, a closed urinary system should be maintained to minimize infection risk. Low-grade suction can be used to ensure that the tubes are draining or that any wound drain is working effectively. Urethral tubes are removed when urinary drainage decreases, usually 10 to 14 days after surgery. The suprapubic tube remains in place for 4 to 6 weeks.

Excessive crying increases intra-abdominal pressure, putting tension on the suture line. Keeping the baby content during the postoperative period is a challenge for both parents and nurses. Parents are encouraged to stay with the child throughout the hospitalization, to promote parent-infant bonding and comfort. Breast feeding is resumed as soon as the infant is able to tolerate a regular diet. Once the child has recovered and the wound is healing well, the child with a cast in place or external fixator can be discharged home until removal of the suprapubic catheter. If traction is still used postoperatively, the child remains in the hospital.

Discharge from Hospital and Management at Home

Many of the children and families live some distance from the treatment center, and good communication with local services is imperative for the operating center. Parents also must become confident in handling their baby, managing normal baby cares while additionally caring for a spica or fixator and urinary drainage tubes that are in place. A written discharge plan should be drawn up between the parents and the treating center. Parents are provided with contact information should an unexpected event happen. Discharge information should include the following:

- Date for return to the treatment center for removal of remaining catheter/cast
- Drug information, analgesia, and also prophylactic antibiotic advice
- Contact telephone numbers for treatment center (24-hour advice line) and local services
- How to manage a blocked catheter, collect a sample of urine, change a catheter bag system, and care for suprapubic site and tube
- What to do if the child develops a temperature
- The purpose of any follow-up investigation and when it will happen (e.g., renal ultrasound)

Community visits can be arranged before discharge, and all appropriate professionals who are likely to care for the child in the community should be informed of the initial diagnosis and management plan for the child. This can include the family doctor, health visitor, home health nurse, or school nurse if the surgery has been undertaken on an older child.

Epispadias Repair

SURGERY

For boys undergoing staged reconstruction, closure of the epispadias defect is usually started between 12 and 18 months of age. The goal is to create a straight penis, achieving the best length possible from the available tissue, with the meatus at the tip of the penis. In some cases, closure of the epispadias defect increases resistance to bladder emptying, resulting in increased bladder capacity or difficulties with voiding. In the United States, epispadias repair is often done on an outpatient basis or with an overnight stay.

DISCHARGE FROM HOSPITAL AND MANAGEMENT AT HOME

As with hypospadias repair, a urethral catheter and dressing are left in place after surgery. The advice and observations suggested for follow-up care are the same.

URINARY CONTINENCE PROCEDURES

The following surgical interventions and associated nursing management relate to children who have a neuropathic bladder, either secondary to a spinal lesion such as spina bifida, sacral agenesis, or a spinal cord injury or as a consequence of a significant birth anomaly such as cloacal exstrophy or high imperforate anus.

Bladder Augmentation

If the child has a small-capacity neuropathic bladder or a high-pressure "risky" bladder, an augmentation is necessary to minimize long-term risk to the upper tracts and to help attain continence. This type of surgery is rarely an emergency; therefore, the admission can be planned and organized for a time that will minimize family disruption. A vesicostomy[31] may be necessary to manage the "at-risk" bladder quickly, but this approach does not offer continence: the urine drains into a diaper or a urostomy bag applied to the stoma.

Essentially, a segment of gut (usually ileum) is augmented into the bladder, or a neobladder is created from gut in the child who has previously had a cystectomy (e.g., after pelvic clearance for tumor). The augmented bladder has a low contractility and therefore can generate high postvoid residuals. Children who undergo a bladder augmentation and will be catheterized urethrally after surgery are taught preoperatively how to perform intermittent self-catheterization. If a child is unable to catheterize via the urethra (due to sensation, urethral anomaly, poor dexterity, or other reasons), a continent stoma can be created at the time of bladder surgery. A continent stoma (Mitrofanoff stoma) is a piece of bowel (appendix or tabularized gut or ureter) that joins the bladder to the abdominal surface, thereby allowing a catheter to be passed into the bladder (see Figure 56-8 in Chapter 56).

As with other surgeries, parents and children will need education and preparation. They will also have to learn new skills before surgery, and changes to their routines need to be considered. These changes include

- Handling of catheters, because hydrophilic catheters can be slippery
- Learning to perform intermittent self-catheterization, which may take the child and parent several weeks to master; the nurse needs to support them during this time
- Knowing how to order equipment they will need postoperatively from community sources
- Storage and disposal of products

- Understanding, by the child as well as the parents, of the consequences of surgery and their responsibility in long-term care and follow-up[32]
- Undertaking bladder washouts after surgery
- Working with the nurse to inform the child's school of changes to the child's toilet routine and the role the school will have in the management of the child's condition

Postoperative Care

The child who has undergone bladder repair will have several tubes in place postoperatively, including the following:

- Nasogastric tube—to allow the bowel to rest after surgery, minimizing risk of ileus
- Cannula—to administer intravenous fluids, because the child will be taking nothing by mouth until bowel sounds return
- Patient-controlled analgesia—to minimize discomfort
- Possibly a wound drain
- Suprapubic catheter—this will stay in place for at least 3-4 weeks
- Possibly a urethral catheter—to ensure adequate bladder drainage
- Possibly ureteric stents if the ureter was moved during surgery
- Catheter to the continent stoma (Mitrofanoff) if one was created at the same time as the augmentation

Discharge from Hospital and Management at Home

Often, the child goes home after recovery from the surgery with only the suprapubic catheter remaining (and the catheter to the continent stoma, if one was created). During this time, the parents undertake bladder washouts to ensure that the catheter is draining freely and to drain the mucus from the bladder.

After 3 to 4 weeks, the child returns to the hospital and the suprapubic catheter is clamped. (The catheter to the continent stoma, if present, will be removed.) The child then begins to self-catheterize via his or her urethra or via the continent stoma. The child may have a contrast study done before starting catheterization, to check the integrity of the augment. Initially, the bladder is emptied frequently, starting at intervals of 30 to 60 minutes; the interval gradually increases over a period of 10 to 14 days until the child is catheterizing every 3 to 4 hours. The child is kept on free drainage at night until a sufficient storage capacity is achieved during the day, to minimize risk of bladder perforation.[32] Some children require catheterization during the night if their urine output at night is greater than their bladder capacity. If the child has a continent stoma, both the child and the parents are encouraged to learn how to catheterize the stoma.

There are a number of key points to remember in the postoperative care of these children:

- Parents need to be taught how to look for complications from surgery, including bladder rupture and acute bowel obstruction.
- Good hygiene and clean procedure for the child and family are encouraged to minimize cross-infection, and non-latex gloves should be used when performing catheterization (when indicated).
- Bladder washouts should be performed (per local policy) to wash out the mucus and to minimize the risk of urinary infection and development of bladder stones.
- The largest catheter possible should be used to drain the urine, depending on the route of catheterization and the age of the child; children with a continent stoma tend to use a size 14 male-length catheter to facilitate good bladder drainage.
- Regular bladder emptying is important, and the child and family should be encouraged to stick to a good routine. Use of an alarm watch or beeper can help the child remember to catheterize. Once the child become more independent, monitoring of bladder emptying can be challenging, but the young person needs to be informed of the risks associated with noncompliance or failure to adhere to medical advice.
- Allowing the bladder to become overly full can result in difficult catheterization. The child and parent need to know what action to take if they are unable to catheterize (via urethra or continent stoma).
- Because many children with neuropathic bladder are at a greater risk of latex allergy, exposure to latex should be minimized. Gloves and catheters should be non-latex. Children and parents should be made aware of the signs of latex allergy and appropriate testing and management techniques.
- The child should be encouraged to wear a medic alert bracelet, which will allow identification of any medical problems if the child becomes unwell.
- The nurse needs to remember that the young person may wish to discuss some issues in private, such as sexual activity and pregnancy issues.
- The child or young person and the parents need to understand the follow-up protocol after bladder augmentation and the need to seek lifelong medical review.

Bladder Neck Reconstruction

Bladder neck surgery is undertaken in children who have a wide-neck bladder anomaly (bladder exstrophy in male and female children) and in those with an incompetent sphincter (some children with spina bifida). It is important before any surgery to the bladder neck is performed that the child be aware of and understand the surgery. For those children who will attain bowel continence naturally, this should be achieved before bladder neck surgery (i.e., bladder exstrophy).

Urodynamic investigation (bladder pressure studies), possibly in conjunction with cystoscopy, will help the physician evaluate the bladder and assess the child's potential for gaining continence. The bladder capacity needs to be sufficient for the child, and the bladder needs to be compliant during both the filling and the storage phase. Bladder neck surgery can be undertaken at the same time as a bladder augmentation.

The surgical approach to bladder neck surgery is described in Chapter 30. However, there are several approaches to bladder neck reconstruction. All surgical interventions to the bladder neck will result in the child's having a suprapubic catheter and urethral stent in place after surgery.

Discharge from Hospital and Management at Home

The parents should be taught how to care for the catheter and stent and when to return to have the urethral stent removed (7 to 10 days after surgery). Parents should be taught how to safely clamp their child's catheter, which they will be asked to do approximately 3 to 4 weeks after surgery. Parents will be asked to do the following:

- Clamp the catheter for short periods, allowing the child to develop a sense of urine in the bladder.
- Once the child is able to pass urine, gradually increase the time interval between voids, building up to a goal of 4 hours. This may take several weeks to achieve.

- Release the catheter if the child experiences any difficulties with voiding.
- Check the residual urine if it is thought that the child is passing only very small amounts of urine but complains of feeling full.
- Leave the catheter on free drainage and collect a urine sample if the child becomes unwell or complains of dysuria or has hematuria.
- Leave the catheter on free drainage at night.
- Contact the hospital team if they have any worries or concerns.

The suprapubic catheter is removed in the hospital once the child can void well (either independently urethrally or via a catheter) and has had a satisfactory repeat ultrasound study. Parents need to be reassured that day continence may take several months to achieve, and night continence may take longer.

Artificial Urinary Sphincter

For some children, a bladder neck repair will not be sufficient to attain continence, and an artificial urinary sphincter (AUS) may be needed. The AUS is a device that is most often fitted in boys inside their body and consists of three segments: a cuff that fits around the urethra, a button that sits in the scrotum, and a reservoir in the abdomen. All components are joined with silicone tubing. Long-term studies exist that explore incontinence in men and women with this device[33] and the quality-of-life outcomes.[34]

Preoperative Care

Education and preparation should be provided, as previously outlined. Additional considerations include the following:

- The child must be physically big enough for the device to fit.
- The child must be mature and motivated to care for the device.
- The child must have sufficient manual dexterity to be able to use the device.
- Many will still have to catheterize, and they should be able to undertake this preoperatively.
- The child (or parents) must be able to make an informed choice, because the AUS can be problematic. Difficulties include infection, erosion, and failure of the device.
- Concordance with treatment is very important. If the child or young person is reluctant to engage, then use of this device is potentially problematic.
- Some surgeons request a pubic shave for adolescent children and skin preparation with an antibacterial wash to minimize infection of the device at insertion.
- Antibiotics will be given as treatment and then prophylactically to minimize the risk of infection until healing is complete.

Young men may have questions in relation to their fertility when they have a device in place, as well as any possible impact on their ability to have erections. Discussions concerning sexuality and activity need to be answered honestly. For some young people, additional psychological support may be necessary.

Discharge from Hospital and Management at Home

A urethral catheter is left in place for 5 to 7 days after surgery, and the AUS is left deactivated. Anticholinergic medication and antibiotics are given along with regular analgesia to minimize discomfort. The groin area may be swollen postoperatively; once this has settled, the pump can be activated. After the AUS is activated, bladder emptying needs to be resumed. The child needs to be encouraged to wear a medic alert bracelet in case of emergency and needs be aware that the device should be deactivated if they need to have an indwelling catheter via their urethra.

Posterior Urethral Valves

Posterior urethral valves (PUV) are an obstructive anomaly in boys and exist on a scale of severity that affects outcome for renal and bladder health. Parents may have questions relating to their child's long-term renal health, continence, and fertility. The child with PUV may be diagnosed with gross hydronephrosis antenatally, in infancy with infection, or in childhood with a history of incontinence. Both the kidneys and bladder can be affected by the obstruction, with unilateral or bilateral renal scarring and possibly a neuropathic bladder. Some boys experience incomplete bladder emptying and may need to learn to catheterize or have a continent stoma formed.

DISORDERS OF SEXUAL DIFFERENTIATION

The concept of gender is complicated and is influenced by many factors, including social influences and expectations as well as biology.[35,36] Complex concepts inform individual sexuality, including gender identity, gender role, and sex.[37] Parents of children born with a disorder of sexual differentiation face a range of treatment options, from early intervention (optimal gender policy[35]) to waiting until the child is able to be involved in the decision-making process (informed consent policy[38]). Parents experience social, moral, and medical dilemmas, all of which have an impact on the parenting experience of supporting, caring for, and protecting their child.[39] These parents should be offered additional support immediately after the birth of their child and throughout infancy and childhood. The nurse should be able to act as both a source of information to these families and their advocate. The debate on how to best support this group continues, and the nurse has a responsibility to keep up to date with regard to new research and practice issues.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 15

TISSUE ENGINEERING IN PEDIATRIC UROLOGY

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The goal of tissue engineering is to restore form and function when tissues are congenitally absent or dysfunctional from physiologic or pathologic processes. Development of this young field draws principally from the remarkable progress made over the past 3 decades in cell biology and materials science. Biologists have discovered the existence and character of progenitor cells, including stem cells, along with mechanisms of cellular migration, differentiation, and proliferation. Information regarding the natural processes by which cells arise, undergo specialization, and arrange into functional systems lends itself to manipulation for the creation of neotissues. Chemists, physicists, and engineers working in the field of material science have developed biomimetic polymers and the means to process them into forms that can be useful for supporting multicellular structures. Marriage of the biologic and physical areas of research has given birth to the field of tissue engineering, which must continue to function as a multidisciplinary endeavor as it progresses beyond its infancy.

The idea of constructing tissues has relevance for every organ in the genitourinary system. Replacing absent, dysfunctional, or diseased bladder tissue would benefit exstrophy patients, bladder cancer patients, and patients with voiding dysfunction as a result of chronic obstruction. Atala and associates[1] made international headlines in 2006 with their work on bladder augmentations constructed from autologous urothelial and smooth muscle cells supported on natural polymers. Similar efforts are being made to engineer replacement tissues for the urethra,[2] penile corporeal bodies,[3] urinary sphincter,[4] ureters,[5] and kidneys.[6]

Historically, reconstructive urologic surgeons have had to rely on nonurologic autologous tissues when faced with a paucity of native material with which to work.[7] Although attempts to restore adequate structure and function with purely synthetic materials have been successful in isolated cases, such as penile prosthetics and artificial urinary sphincters, most have failed to yield adequate results. Harvesting nonurologic tissue presents risks to the native system, adds to operative morbidity, and requires tissues to perform as they were not evolutionarily designed. The use of bowel to reconstruct bladders or ureters may produce metabolic disorders,[8] diarrhea,[9] stone formation,[10] infections,[11] increased risk of neoplasm,[12] and excess mucus production,[13] all of which result from the shortening of the bowel and its non-natural state of being in contact with urine. Nonetheless, the use of bowel in reconstructing the urinary tract remains a mainstay for surgeons.

Given the long list of disadvantages associated with current reconstructive practices, the interest in using new technology for tissue engineering seems obvious. Because purely synthetic materials have not produced an acceptable alternative, the approach of combining advanced materials with cell-based technologies has emerged as the state of the art for this endeavor.

Urologists are not alone in the need for neotissues for reconstructive purposes. Plastic surgeons,[14] vascular surgeons,[15] and orthopedic surgeons[16] have provided data. Pooling the latest information suggests that the most promising strategy is to couple living cells with synthetic, natural, or hybrid polymer structures. This chapter discusses the latest research in biomaterials, cell culture and growth, and the engineering aspects of designing neotissues for the benefit of urologic reconstruction.

BIOMATERIALS

Living organisms, particularly humans, represent the pinnacle of chemical self-assembly with cells forming from an array of biomolecules and complex cellular arrangements arising from a single cell. The extracellular matrix (ECM) has long been appreciated for its role in serving as the scaffolding that permits three-dimensional positioning of cells into tissues and, subsequently, organs. More recently, a greater awareness has developed for the importance of the ECM in cellular differentiation, migration, and proliferation.[17] A cell must "know" where to go, what type of cell it should become, and what function it should perform when it reaches its proper position. The ECM participates in all three of these processes, and should be viewed as an extension of the cytoskeleton, rather than acting as a simple scaffold.[18] Entrapped growth factors and oligopeptide moieties interact with transmembrane receptors on the cell surface to initiate intracellular biochemical cascades that affect a cell's behavior. These pathways include effectors on the cell's nucleus, which influence movement, growth, and production of specialized products. Basic research into embryologic development[19] and wound healing[20] elucidated the interdependence between construction and degradation of ECMs and the cellular components of biologic tissues.

Construction of man-made biologic tissues requires a strategy that provides a functional substitute for the ECM. With particular attention to polymer-based systems that provide support for the growth and development of specific cells, several aspects of chemical and engineering design must be considered. Primarily, a candidate material must be biocompatible and elicit a negligible immunogenic response from the host. Because permanently implanted materials pose long-term risks for infection, rejection, and untoward migration, most currently studied materials are designed to be biodegradable. The rate of degradation must be appropriate to allow the cellular components to develop sufficient structural integrity. Until this process is complete, the biomaterial must retain biomechanical properties specific to the tissue that it is replacing.[21] A polymer scaffolding for a bladder substitute would have to maintain an adequate amount of distensibility over its useful lifetime.

Because most methods for tissue engineering involve a cellular component, more complex issues have arisen regarding the interaction between the cells and the supporting materials. Implantable substances widely used today were simply designed to minimize the disturbance to surrounding tissues. Ureteral stents have to resist stone formation, and penile prosthetics must minimize local inflammatory responses. A greater sophistication is required, however, if the goal is to integrate cells within the matrix of the biomaterial. In contrast to currently available materials, which interact nonspecifically with biomolecules and cells, newer innovations require that the cell-surface interaction rely on specific mechanisms as they do in vivo with the ECM.[22] When surface contact is made, cells must appropriately migrate, remain viable, and proliferate according to particular signals that are incorporated within the material.

In the following sections, the essential issues of biomaterial design with regard to biocompatibility, biodegradability, cellular adhesion, migration, and proliferation are addressed, and a brief overview of manufacturing processes is presented. As an illustration of the overall paradigm, specific examples of materials relevant to urologic research are discussed.

Biologic Response to Biomaterials

Regardless of the type of material implanted into the human body, the initial response to what is essentially a traumatic injury is nonspecific.[22] Blood from injured vessels and fluid from damaged cells come into contact with the surface to form a biofilm consisting of fibrin and inflammatory products released by the complement system, activated platelets, and inflammatory and endothelial cells.[23] This biofilm, which seems to depend on the material's chemistry and surface morphology, acts as the stimulus for acute and chronic inflammation processes, and ultimately determines the extent of tissue granulation, foreign body reaction, and development of a fibrotic capsule. The intensity and time duration of these responses determine the severity of the perturbation from homeostasis caused by the material, and define the material's biocompatibility.[24]

Acute inflammation begins within minutes after implantation as leukocytes accumulate at the solid-liquid interface.[23] Neutrophils predominate initially, but are short-lived, whereas monocytes differentiate into macrophages, which can populate the surrounding tissues for weeks or months. Adhesion of neutrophils and macrophages to artificial materials lacks the specificity displayed during inflammation of native tissues. Opsonins, particularly IgG and the complement-activated fragment C3b, present in the adsorbed biofilm are recognized and bound by cell surface receptors on the leukocytes, entrapping them.[25] Under most circumstances of inflammation, attachment of neutrophils and macrophages initiates the process of phagocytosis. In the specific case under discussion, however, the biomaterial is too large for engulfment and killing or degradation to occur. Instead, a process of frustrated phagocytosis occurs whereby the leukocytes, along with activated platelets, release chemotactic agents for the recruitment of fibroblasts, mitogens, proteases, and oxygen-derived free radicals.[26] Macrophages play a central role in tissue resolution or organization depending on the type of tissue involved and the nature of the implanted device.[27]

During the initial phase of inflammation, the process of granulation begins, and then there is competition between two physiologic pathways. Chronic inflammation predominates when inflammatory stimuli persist, as a result of the physical and chemical properties of the material, or if there is continuous motion of the device leading to repetitive local trauma. Cellular products from the macrophage recruit lymphocytes and plasma cells that are responsible for the humoral and cell-mediated response.[28] Although these components of the immune system are important to the overall biocompatibility of a material, the mechanism of how they react to foreign bodies is still poorly understood.

In normal wound healing, formation of granulation tissue begins 1 day after a traumatic event, and the characteristic appearance becomes visible after 3 to 5 days. Extracellular matrices of proteoglycans and then collagen are produced by fibroblasts, and neovascularization starts as endothelial cells proliferate, mature, and organize into new capillaries.[29,30] A foreign body reaction occurs within the granulation tissue as macrophages react to their inability to phagocytize the foreign material. The immobilized macrophages, in response to secreted lymphokines, fuse to form multinucleated foreign body giant cells.[31] Foreign body giant cells persist as long as there is an inciting agent present and have been seen in tissue surrounding devices 20 years after their implantation. They secrete degradative enzymes and reactive oxygen species that seem to play a role in the resorption of biomaterials, analogous to the role of osteoclasts in the remodeling of bone.[32]

Different implantable devices show wide variation in the extent of the foreign body reaction. Silicone breast implants with very smooth surfaces have layers of macrophages that are only one to two cells thick,[33] whereas implanted expanded polytetrafluoroethylene vascular prosthetics with very rough surfaces have much thicker reactive zones with high populations of macrophage and foreign body giant cells.[34] Optimization of surface morphology can minimize the foreign body reaction and serve as one controllable variable in manipulating tissue repair around implantable devices.

The end result of the healing process leads to either resolution with complete restoration of normal cell architecture and function or organization with fibrosis as is seen with most biomaterials. In part, the end result is determined by the nature of the surrounding parenchymal cells, which may normally proliferate (labile), have proliferative capacity in response to injury or other stimuli (stable), or be incapable of proliferation (permanent). Cells of the third type (e.g., nerve, cardiac, or skeletal muscle cells) invariably resolve the inflammatory exudates and undergo fibrosis. Tissues formed from labile cells, such as endothelial or hematopoietic cells, or tissues from stable cells, such as kidney or smooth muscle, theoretically can heal with perfect resolution under favorable circumstances. Manipulation of the material's chemistry, surface physics, and processing method aims to control the nature of the adsorbed biofilm, extent of inflammation, and ultimate fate of the healing response.

Cellular Migration, Differentiation, and Proliferation in Biomaterials

The previous section describes nonspecifically the body's reaction to implanted foreign material and serves as a starting point for how we go about constructing matrices to support a cellular component. Control of the initial surface recognition and subsequent inflammatory reaction must allow us to have specific cell types incorporate within the polymer and, in some cases, differentiate appropriately. The material must direct migration of the cells and support their viability when incorporated. Exact details of how to go about this process are lacking; however, observation of natural systems has already produced enough information to permit successful construction of cell-supporting polymer matrices.

At its most functional simplicity, the ECM acts as a scaffold through which cells move and attach themselves. Insoluble adhesion molecules bound to the natural polymers serve as attachment points to allow cells to "push or pull" themselves along and then arrange themselves at fixed locations. Such molecules include fibronectin, collagen, vitronectin, and laminin, all of which contain peptide sequences such as RGD (arginine-glycine-aspartate) that bind to integrins on cell surfaces.[35] The transmembrane integrin molecule mediates interaction between the ECM and the cytoskeleton through the activation of biochemical cascades involving protein kinase C, mitogen-activated protein kinase, and the GTPases, Rac and Rho.[36] Instead of acting as a passive support structure, the matrix actively stimulates cell adhesion and migration through these biochemical pathways.

Migration also depends on the gradients of soluble molecules that act as chemoattractants and growth factors. The ECM serves to concentrate these factors in specific locations, protect them from proteolytic degradation by providing stearic interference, and possibly enhance receptor-ligand recognition. Important soluble molecules include the transforming growth factor-β superfamily of proteins (e.g., bone morphogenetic proteins, fibroblast growth factors, Wnt proteins, hedgehog proteins, and Notch ligands).[37] In addition to their role in migration, these signal moieties play a role in the cellular differentiation and proliferation. Incorporation of these signals into biomaterials is one strategy for promoting the incorporation, differentiation, and proliferation of cells into synthetic or semisynthetic polymers.

The mechanism of cellular movement through a polymer matrix depends on the nature of the material and the cell. If the pore size between insoluble fibers is sufficiently large, the fibers are sufficiently pliable, or the cell can adaptively alter its shape, degradation of the matrix is unnecessary.[38] In most natural ECMs, however, cell migration depends on proteolysis to provide adequate space for mobility. Cells secrete matrix metalloproteases and serine proteases to degrade the polymers locally.[39] To maintain structural integrity, the action of these proteases must be carefully balanced by the action of their inhibitors, such as tissue inhibitors of metalloproteinases. Biodegradation is not only important for the resorption of artificial biomaterials but also may provide a mechanism for temporal and spatial presentation of soluble growth factors. As cells invade and proteolyze a polymeric biomaterial, growth factors that have been incorporated during the synthetic process may be released to enhance migration and proliferation further.

Any attempt at tissue construction beyond a few cells thick must address the issue of creating a concomitant blood supply. Angiogenesis results from de novo construction by endothelial precursor cells or by sprouting from preexisting capillaries.[30] These processes are under control of a biochemical cascade involving vascular endothelial growth factors, fibroblast growth factors, transforming growth factors, angiopoietins, and other chemokines.[40] Incorporation of vascular endothelial growth factor into fibrin matrices has been proven to invoke the production of new blood vessels by invading endothelial cells.[41]

Synthetic, Naturally Derived, and Acellular Tissue Matrices Used as Biomaterials in Urologic Tissue Engineering

A single universal biomaterial for use in tissue engineering does not exist and, given the wide range of applications, probably never will. Investigators to date have used materials that are synthesized wholly in the laboratory, are derived from natural systems, or are produced from harvested tissues that are stripped of their cellular component. Each has advantages and disadvantages, but all contribute to the knowledge required to develop more optimal materials.

The most used and studied materials to date are the synthetic poly (α-hydroxy) acids, such as polyglycolic acid (PGA), polylactic acid, and their copolymers, such as poly-DL-lactide-co-glycolide (PLGA).[42] These polyesters form stable hydrogels that can be manufactured in unlimited quantities into fibers and formed into useful shapes to serve as scaffolding for neotissues. They have good mechanical strength and are broken down by hydrolytic cleavage of their ester groups to nontoxic, easily metabolizable products. A disadvantage for these compounds is that they produce acidic products after degradation, which, despite being in such low quantities so as to be nontoxic systemically or regionally, may have untoward effects on developing cell structures within the matrices.[43] Also, although the degradation rates can be manipulated by changing the polymer sizes and processing parameters, they still do so by bulk degradation that can produce abrupt and unwanted changes in mechanical integrity. Finally, these polymers lack specific bioactive moieties to control biologic interactions at their surfaces and subsequently cell migration in the bulk of the matrix. Despite these drawbacks, they are one of only a few materials approved by the U.S. Food and Drug Administration (FDA) for use in humans and have been and will continue to be in widespread use.

Naturally derived materials are materials obtained by or, as synthetic capabilities advance, at least inspired by naturally occurring compounds. These include the major ECM components collagen and elastin, and alginate and chitosan.[44,45] Collagen is a major component of ECMs, consisting of superhelices of polypeptides arranged into fibers. Each polypeptide has a glycine every three residues and is proline-rich with many of its residues amino hydroxylated through post-translational modification. Different mechanical properties are obtained by altering covalent and noncovalent interactions between the collagen fibrils. Elastin is also formed from α helices, but these are able to stretch reversibly. Cross-links between helices via a four-lysine bridge result in a remarkably elastic material. Alginate, derived from seaweed, and chitosan, a modification of the crustacean shell component chitin, have important peculiar traits that make them useful for specific biomaterial functions.

The major advantages of collagen or elastin for biomaterial applications are that these compounds have been evolutionarily designed for the express purpose of supporting cellular tissues. They are biodegradable and can be modified to produce a large spectrum of biomechanical properties. Also, cells have specific means to interact with sites within these polymers. Now that they may be synthesized from chemical or modified microorganisms,[46] the risk of pathogen transmission and difficulty in obtaining natural biologic tissues is less of an issue. The optimal synthesis and design of collagen and elastin has yet to be realized, however. These materials must be modified (e.g., by cross-linking) to inhibit enzymatic degradation, and their specificity with particular cell types needs to be enhanced through the incorporation of new bioactive sites.[47] Combining genetic engineering methodology with state-of-the-art polymer synthesis, these biologically inspired compounds should prove useful, albeit in some modified form.

The aforementioned materials do not approach the complexity of natural ECMs in their ability to interact specifically with cells at the biointerface or contained within their matrices. Because understanding of cellular-ECM interactions is still incomplete, several researchers have chosen to circumvent these obstacles by taking these native materials directly from the source. Two examples in the urologic literature include small intestinal submucosa (SIS), processed from porcine jejunum, and bladder submucosa, derived from porcine bladders.[48] The former is approved by the FDA and commercially available for pubovaginal slings, grafts for repair of Peyronie disease, and various other nonurologic procedures. SIS is mainly composed of collagen and contains bound glycol proteins, such as fibronectin and laminin, which promote specific adhesion and growth of epithelial cells and fibroblasts. Glycosaminoglycans, such as heparin, hyaluronic acid, chondroitin sulfate, and dermatan, also are found within the matrix. These moieties stimulate collagen deposition, angiogenesis, and cell differentiation via their interactions with several growth factors. Acellular tissue matrices derive further versatility when hybridized with synthetic polymers, such as PLGA, to optimize their biomechanical properties and allow for better control of their microarchitecture.[1]

The disadvantages of these materials include a theoretical risk of pathogen transmission owing to viruses or prions, heterogeneity in performance because of nonuniform synthesis and processing, and relative difficulty and expense with large-scale production.[49] Despite the drawbacks, acellular tissue matrices offer a level of biomimicry that is unlikely to be obtainable through synthetic means for years to come, and they are likely to play an increasing role in tissue engineering in the foreseeable future.

The challenge for materials chemists is to develop polymers that can be produced precisely and reproducibly in large quantities that have the biomechanical, toxicologic, and biochemical specifications of the naturally occurring ECMs. Peptide-based, elastin-like, and "smart" polymers, and carbon nanotubules are some modern developments that may come to the fore in this rapidly progressing field.[50,51]

Synthetic and Processing Methods

In simplest terms, tissue engineering techniques have followed two generalized strategies. In the first strategy, a biocompatible matrix is implanted into the body where the host cells incorporate, proliferate, and reconstitute new tissue. In the second strategy, cells from the host or donor are incubated with the biomaterial in vitro and implanted as a cellularized matrix. Synthetic and processing methods for either case share common aspects with a few notable differences.

Regardless of which stage in the process cell incorporation occurs, the surface chemistry, roughness, and porosity play a crucial role. Nonspecific adsorption results in the formation of a biofilm with denatured proteins and cells of questionable viability.[52] This biofilm may produce more severe inflammatory reactions and form a barrier that limits incorporation of desired cells. The goal is to prevent this nonspecific adsorption while presenting a means for specific cell adhesion and migration. Nonfouling surfaces to meet these goals have been constructed, the most studied of which consist of polyethylene oxide.[53] Polyethylene oxide is a hydrophilic polymer that can be incorporated into the base matrix, covalently attached to the surface, or adsorbed onto the surface. The individual polymer chains have minimal affinity with natural biomolecules, and their "ruglike" pattern at the solid-liquid interface provides a stearic barrier for molecular and cellular adsorption onto the base matrix. A negative aspect of polyethylene oxide is that its action depends on the surface density of the polymer chains, which are susceptible to damage via oxidation. More novel approaches, such as phospholipid surfaces,[54] saccharide surfaces,[55] and peptide-based polymers,[56] may prove more robust and, it is hoped, perform more consistently in in vivo environments.

Prevention of nonspecific adsorption to polymer surfaces permits the possibility of creating specific mechanisms of interaction between biomolecules and cells with the biomaterial. Incorporation of bioactive moieties within the biopolymer and at its interface has been achieved successfully in several studies. One of the most commonly employed bioactive moieties is the RGD oligopeptide, which serves as a ligand for cell membrane–bound integrins. RGD has been used to modify the surface of polylysine/polyethylene glycol copolymers to promote adhesion of fibroblasts.[57] If the glycine peptide is converted to alanine and made into peptide polymers, the result is a matrix consisting of β-sheets that can adopt a variety of macrostructures and is able to support the adhesion and growth of rat neuronal cells.[58]

In addition to oligopeptides, whole proteins have been used to promote cell adhesion. Adsorption of osteopontin onto polyhydroxyethyl methacrylate along with collagen[59] and modifying gold thiol-alkane surfaces with fibronectin[60] promoted the adhesion and viability of endothelial and osteoblast cells. The engineering of bioactive sites can extend from the surface and into the bulk matrix as well. Covalent attachment to protease-sensitive segments of polyethylene glycol polymers promoted endothelial cell migration and neovascularization within the matrix.[61] As suggested by these examples, combining bioreactive sites within the polymer, covalently attaching insoluble agents, and trapping diffusible signal molecules would optimize the adhesion, incorporation, differentiation, and proliferation of the cellular component of engineered tissue.

A useful method for incorporating cells and entrapping soluble agents into a polymer matrix exploits the process of self-assembly.[62] Polymers can be manufactured with specific interacting side groups to induce secondary, tertiary, and quaternary structures that are familiar in natural biopolymers. Currently, several polymer types exist that adopt a random, chaotic structure on one side of a critical temperature or pH, but arrange themselves into orderly matrices on the other side of the cutoff point.[50] Similarly, photoreactive polymers may adapt specific configurations depending on the wavelength of light to which they are exposed.[50] One could incubate fibroblasts, smooth muscle cells, or stem cells with a polymer that has an open structure at room temperature, but that adopts an orderly structure when warmed to 37° C. This strategy has already been successful in creating time release mechanisms for pharmacologically active compounds that are entrapped in gels and then able to diffuse externally in vivo. Self-assembling polymers also lend themselves to injectable materials that are liquid at room temperature and form matrices at body temperature.[63] Bulking agents, such as cross-linked collagen and Deflux (Q-Med, Scandinavia, Inc., Princeton, NJ), are already used for anti-incontinence and antireflux procedures, but could be enhanced by applying tissue engineering principles.

Although many of the biophysical properties of biomaterials depend largely on the material's chemistry, important parameters such as pore size, fiber thickness, and surface roughness depend critically on the manufacturing process. Borrowing heavily from industrial experience, notably from the production of textiles, several methods are being developed to control the performance of the finished product better. For example, conventional methods to create polyester matrices result in micrometer-scale fibers that do not allow incorporated cells to adopt a physiologically normal structure.[35] Their large size causes the cells to flatten out and may impede normal migration and growth. Fabrication of nanometer-scale fibers from electrospinning now allows polyester fibers to approximate more closely the size of naturally occurring biofibers.[64] A general group of techniques known as solid free form fabrication has been developed from the nanotechnology sector, which is perhaps the most promising area in materials processing.[65] Essentially, these methods use computer-aided design software in conjunction with sacrificial molds and nanofabrication equipment to construct three-dimensional structures in layer-by-layer fashion.

Techniques including three-dimensional printing, stereolithography, fused deposition modeling, and three-dimensional plotting allow for unprecedented control over the microarchitectural design of biomaterials. Technologic advances in bioengineering and advances in polymer chemistry and molecular biology offer great potential for intelligent design of semisynthetic neotissues for clinical applications.

CELLULAR COMPONENTS

Choices for cells that can be used in tissue engineering and regenerative medicine include mature, differentiated native cells and stem cells. Stem cells include adult and embryonic stem cells, and other progenitor cells with probably a more limited, but not yet completely defined potential. This is exemplified by animal studies (described later) that have used cell therapies based on progenitor cells. Cells used in urologic tissue engineering need to achieve the stringent characteristics of the highly specialized urothelium and the skeletal and smooth muscle tissue that compose the various organs of the urinary system.

Native Cells

Urothelium

The urothelium is stratified and displays a regular, polarized architecture of increasing morphologic complexity and differentiation from base to surface.[66] It is composed of basal, intermediate, and superficial cells. Basal cells are small (approximately 10 µm in diameter), form a single layer, and serve as precursors for the other cell layers. Intermediate cells are piriform in shape, are 10 to 25 µm in diameter, and form a layer of variable thickness. The highly specialized superficial or "umbrella" layer comprises very large, hexagonally shaped cells with diameters of 25 to 250 µm. The umbrella cells have a long half-life; however, they are rapidly regenerated when the urothelium is damaged. This regeneration can result from cell division within any of the three cell layers, and generation of the multinucleate umbrella cells is likely the result of intermediate cell-cell fusion.[67]

The umbrella cells have a unique, highly specialized surface membrane containing thickened plaques of asymmetric unit membrane that represent the primary transcellular urinary barrier. The asymmetric unit membrane plaques are formed by the interactions of four membrane proteins—uroplakins Ia, Ib, II, and III—which are useful markers of terminal urothelial cytodifferentiation.[68] Urothelial cell layers can be characterized by staining against markers of epithelial differentiation. Symplekin (a marker of tight junctions), uroplakins, and cytokeratin 20 are found exclusively in superficial cells, whereas other cytokeratins, such as CK7, CK8, CK13, CK17, CK18, and CK19, are expressed in basal and intermediate urothelium.[69]

Skeletal Muscle

The contractile unit of adult skeletal muscle is the myofiber, a highly specialized syncytial cell containing hundreds of postmitotic myonuclei within a continuous cytoplasm. Repair and maintenance of myofiber is attributed to a pool of undifferentiated myogenic precursors or satellite cells, located beneath the basal lamina of myofibers.[70] In mature skeletal muscle, these cells are normally in a quiescent state, and they can be activated in response to muscle damage or disease.[71] Satellite cells, when activated, express myogenic markers and regenerate damaged myofibers. Satellite cells can be defined by their position and functionally, by the expression of specific proteins such as M-cadherin, c-Met, Pax7, the adhesion molecule N-CAM, CD34, and the myogenic regulatory factor Myf5.[72] More recent studies suggest that after activation and proliferation, a few satellite cells switch from terminal myogenesis to maintain the pool of progenitor quiescent satellite cells.[73] For these characteristics of self-renewal and their capacity to regenerate injured muscle, satellite cells may be considered "stemlike" cells in mature skeletal muscle.[74]

Smooth Muscle

In contrast to striated muscle, smooth muscle cells retain a multifunctional capacity for contraction, migration, proliferation, synthesis of ECM components, and secretion of growth factors and cytokines. Each phenotypic state is characterized by expression of a unique set of structural, contractile, and receptor proteins and isoforms that correlate with differing patterns of gene expression.[75] A striking feature of smooth muscle biology is the considerable heterogeneity in the origin of smooth muscle cells. During embryogenesis, their precursors arise from three different lineages: mesenchymal cells, neural crest cells and epicardial-derived cells.[76] This confers the regional specificity required of them to adapt to tissue-specific needs and is reflected in their varying gene expression patterns that can be used for tissue engineering purposes.

Stem Cells

Adult Stem Cells

Adult stem cells such as bone marrow stem cells have been used effectively in clinical practice for replacement after ablative therapy in malignancies. These adult stem cells were thought to have the potential for transdifferentiation, or the ability to cross tissue lines and regenerate other tissue types. More recent studies have shown, however, that these cells are unable to acquire other phenotypes. The presence of twice the normal amount of DNA content in transformed adult stem cells suggests cell fusion rather than transdifferentiation, casting serious doubts on their plasticity.[77-79]

Embryonic Stem Cells

Two main embryonic sources of human stem cells were described in 1998.[80,81] Human embryonic stem (hES) cells are derived from the inner cell mass of the blastocyst stage embryo, and human embryonic germ (hEG) cells are obtained from primordial germ cells populating the gonadal ridge of 5- to 9-week postfertilization human embryos. The hEG cells are similar to hES cells in their pluripotentiality and self-replication ability. They share several important characteristics, including high levels of intracellular alkaline phosphatase, presentation of specific cell markers, growth as multicellular colonies on feeder layers, normal and stable karyotypes through multiple continuous passages, and the capability to differentiate into cells of all three embryonic germ cell layers.

Formation of embryoid bodies is an important intermediate step for hES and hEG cells, before differentiation into various cell types. With embryoid body formation, the markers of pluripotentiality decline, and ectodermal, mesodermal, and endodermal markers appear. Using various culture conditions and growth factors at this stage, researchers have successfully differentiated mammalian embryonic stem and embryonic germ cells into neurons, glial cells, cardiomyocytes, vascular endothelium, muscle cells, and endodermal derivatives.[82-86] Owing to difficulties in maintaining undifferentiated hEG cells in culture, however, cell lines have been derived from hEGs after embryoid body formation, termed embryoid body–derived (EBD) cells.

Although EBD cells do have a stable karyotype and are capable of long-term, robust proliferation in culture, they differ from hES and hEG cells in that they do not require feeder layers, are not immortal, and do not form teratomas when implanted in an immunocompromised animal. Several such cell lines have been established from hEG-derived embryoid bodies, and mixed cells and clonally isolated lines have been shown to express various developmentally distinct markers.[87] Pluripotential stem cells derived from hES cells and hEG cells can differentiate into any tissue,[82,87] regenerate rapidly, and be used even when native bladder tissue is unavailable. Smooth muscle differentiation of mouse embryonic stem cells[83] and hematopoietic and neural differentiation of hES cells have been reported.[84,85] hEG cell derivatives have facilitated neurologic recovery in paralyzed rats with experimentally induced motor neuron disease.[88]

Using markers of differentiated smooth muscle such as actin (SMA-α) and myosin heavy chain (SM-MHC), Lakshmanan and associates[89] selected EBD cells derived from hEG cells, and characterized and co-cultured them with human urothelial and smooth muscle cells on commercially available porcine SIS. These hEG-derived cells were found to be positively chemotactic in co-cultures with human bladder smooth muscle and urothelium.[90] Frimberger and colleagues[91] showed that hEG-derived cells cultured on SIS had the ability to regenerate bladders in a nude rat model of partial cystectomy. Viable hEG-derived cells were identified in vivo for 4 weeks using lipophilic dyes. Factors affecting in vivo survival and differentiation of these cells remain to be elucidated.

UROLOGIC TISSUE ENGINEERING

Bladder

Immune rejection is avoided when native cells are harvested from the patient, expanded in vitro, and returned to the patient. This method was shown to be feasible in a canine model of bladder replacement, in which urothelial and smooth muscle cells were obtained from small bladder biopsy specimens and expanded in tissue culture. These cells populated a biodegradable bladder-shaped synthetic polymer matrix of PGA, coated with a liquefied copolymer, PLGA. After in vitro growth for 4 to 5 weeks, the tissue-engineered bladder was used to augment the donor canine bladders. Good compliance of the engineered bladders was recorded 11 months after surgery compared with controls.[92] These investigators showed that a similar process was feasible in humans, by using tissue-engineered autologous bladders in seven patients with myelomeningocele, who required augmentation cystoplasty.[1] The scaffolds used were different from the canine study, with decellularized bladder submucosa for the first four patients, and a composite of collagen and PGA for the last three patients. Although the postoperative urodynamic data were not impressive, this study sets the stage for future urologic tissue engineering efforts.[93]

This strategy has some other drawbacks, including lack of native bladder tissue in congenital disorders and malignancies, and the limited regenerative potential of fully differentiated, mature cells, even if available. Of particular importance is the impact of in vitro cell culture on the functional capacity of mammalian cells, and the possible interspecies variation. These factors have to be accounted for when extrapolating animal experimental results to human subjects, especially when extended periods of cell culture in vitro are necessary. Cultured human detrusor smooth muscle cells maintain their morphologic and biochemical characteristics up to three passages. Further passages in culture result in progressive loss of α-actin immunoreactivity, and possibly muscarinic receptor subtype expression downregulation.[94] In the mouse model, SMA-α expression correlates with bladder smooth muscle contractility.[95] It may be preferable to restrict such experiments to early passage cells. Compared with smooth muscle cells obtained from functionally normal human bladders, the phenotypic and functional characteristics of smooth muscle from exstrophic and neuropathic bladders were normal, by immunocytochemistry, by histology, with organ bath studies, and with Western blot analyses.[96] These cells were evaluated after seeding on PGA/PLGA matrices for up to 2 months. With different contractility assays, however, human neuropathic bladder–derived muscle cells were significantly less contractile than normal cells.[97] They also were more proliferative, and less adherent, despite similar morphologic characteristics.

These varying results highlight that form does not always equate to function, and morphologic assessments alone are insufficient. Standardized culture conditions and contractility assays are needed to compare functional efficacy of different in vitro culture techniques, an essential step in the process of assessing cells from different sources.

Urinary Rhabdosphincter

Strasser and associates[98] reported the first clinical study of cell therapy–based treatment of sphincter insufficiency using muscle-derived stem cell transplantation in patients with stress urinary incontinence. More recently, these investigators reported randomized clinical trials comparing the effectiveness of ultrasound-guided injection of autologous myoblast and fibroblast with standard endoscopic injection of collagen for treatment of stress urinary incontinence.[4,99,100] Their results confirmed the efficacy and safety of cell-based therapy to improve the structure and contractile function of sphincter.

In the first North American clinical trial of cell-based therapy for incontinence, transurethral or periurethral injection of autologous muscle-derived cells was used to treat stress urinary continence in eight women.[101] Three patients received a repeat injection after 6 months. The injection of muscle-derived cells in this pilot study showed no short-term or long-term adverse events. A multicenter study to investigate a muscle-derived cell dose-response is now ongoing.

Kajbafzadeh and colleagues[102] investigated autologous muscle precursor cell injection in recovery of external urethral sphincter function in five children with the exstrophy-epispadias complex and urinary incontinence. During 4 months of follow-up, incontinence score improved in four children; a girl with very short urethral length and fibrosis had no change in continence status. This study suggested a potential new therapeutic approach for incontinence therapy in patients with the bladder exstrophy-epispadias complex.

Ureter

Matsunuma and coworkers[5] investigated the efficacy of the ureteral decellularized matrix as a scaffold material for a tissue-engineered ureter, and the effect of bone marrow–derived mononuclear cells on the neovascularization of the scaffold in a canine model. Urothelial cells were obtained from canine bladders, cultured, and seeded onto the inner surface of the ureteral decellularized matrix before transplantation into the subcutaneous space of nude mice or the omentum of nude rats. To facilitate neovascularization and survival of urothelial cells in the implant, bone marrow–derived mononuclear cells were seeded around the matrices before transplantation. This study showed that the ureteral decellularized matrix is a useful scaffold for a tissue-engineered ureter, especially when seeded with bone marrow–derived mononuclear cells to enhance angiogenesis.

Urethra

Bhargava and colleagues[2] developed a tissue-engineered buccal mucosa for use in substitution urethroplasty. In this study, oral keratinocytes and fibroblasts were isolated from the epidermis and dermis of buccal mucosa. These cells were seeded on the de-epidermized dermis to create a full-thickness buccal mucosa. Histologically, the tissue-engineered buccal mucosa closely resembled the native oral mucosa and was suitable for clinical use.

Penile Tissue

Kwon and coworkers[3] reported the possibility of replacing an entire cross-sectional segment of both corporeal penile bodies with autologous engineered tissues in rabbits. Autologous corpus cavernosal smooth muscle and endothelial cells were harvested, expanded, and seeded on the acellular collagen matrices. An entire cross-sectional segment of rabbit phallus was excised and interposed by engineered matrices. The experimental corporeal bodies showed intact structural integrity on cavernosography, and histologically sinusoidal spaces and walls lined with endothelial and smooth muscle cells were observed in the engineered grafts. Grafts without cells contained fibrotic tissue and calcifications with sparse corporeal elements. This study showed that autologous engineered corporeal collagen matrices can form corpora cavernosa tissue structures in a rabbit model.

CONCLUSION

There is undoubtedly a need for urologic tissue substitutes, either engineered or regenerated, or a combination thereof. The amalgamation of advances in biomaterial science and cell biology, with pediatric urologists as catalysts, should prove to be an exciting and rewarding time for research in this nascent field.

REFERENCES

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PART II

KIDNEY

CHAPTER 16

ABNORMAL MIGRATION AND FUSION OF THE KIDNEYS

Mark Woodward and J. David Frank

EMBRYOLOGY

A comprehensive description of the embryology of the kidney is provided in Chapter 1. In brief, the kidney develops around the 4th week of gestation as a result of an interaction between the mesonephric duct–derived ureteric bud and the metanephros, the most caudal part of the nephrogenic cord. Between 4 and 8 weeks, the kidney ascends in a cephalad direction and undergoes a 90-degree axial rotation from horizontal to medial. At the same time, the ureteric bud divides sequentially to form the pelvicalyceal system. During the process of ascent, the kidney receives its blood supply from local vessels—initially median sacral, then common and inferior mesenteric, and finally aorta and vena cava.

Incomplete, excess, or abnormal ascent results in an ectopic kidney. Renal fusion may occur if the kidneys come into contact during the process of ascent.[1]

ABNORMAL MIGRATION: RENAL ECTOPIA

Failure of normal cephalad ascent results in renal ectopia, which may arise as a result of abnormalities of the ureteric bud or metanephros, an abnormal vascular supply, or genetic abnormalities. Data from autopsy studies suggest that renal ectopia occurs in approximately 1:1000 people with an equal sex distribution.[2] There is a threefold increased incidence in unrelated subjects in parts of Kenya, raising the possibility of an as-yet-undefined environmental factor.[3] Only 50% of ectopic kidneys are recognized clinically.[4,5]

Ectopic kidneys may be pelvic, iliac, thoracic, or crossed (Table 16-1), and are rarely normal. They are often small, lobulated, and abnormally rotated with extrarenal calyces and an irregular vascular supply (Fig. 16-1). These anatomic abnormalities may predispose to the higher incidence of pelviureteric junction (PUJ) obstruction and nephrolithiasis seen in this condition.

Diagnosis

The diagnosis of renal ectopia may be suspected antenatally, especially if hydronephrosis is also present. Routine abdominal and pelvic ultrasound for another indication may result in an incidental diagnosis of renal ectopia. Vesicoureteric reflux is associated with an incidence of 30% for unilateral renal ectopia and 71% for bilateral renal ectopia,[9] and routine investigations after urinary tract infection may result in the diagnosis.

If obstruction is suspected on ultrasound, drainage may be assessed using a Tc 99m MAG3 renal scan, but the areas of interest must be appropriately selected. Occasionally, computed tomography (CT) or magnetic resonance (MR) urography may provide additional information.

Additional malformations of the contralateral kidney or cardiovascular, respiratory, urogenital, or skeletal systems are common (Table 16-2).[10,11] Genital malformations in women may cause problems during menstruation, conception, and pregnancy.

Outcome

Patients do not require intervention for renal ectopia, unless they develop a complication. The natural history of vesicoureteral reflux in ectopia seems to be similar to vesicoureteral reflux in normal kidneys with spontaneous resolution to be

Table 16-1 **Types of Renal Ectopia**

Type	Incidence	Location	Notes
Pelvic	Most common	Below aortic bifurcation; L>R; 10% bilateral[6]	May be sole kidney
Iliac	Rare	Above iliac crest but below L2	Similar to apoptotic kidney, but ureter usually short and kidney not mobile and malrotated
Thoracic	Rarest—approximately 1:16,000	Thoracic cavity (Fig. 16-2)	Possibly related to persistent nephrogenic cord[7]; rarely associated with heart, lung, and spinal anomalies including congenital diaphragmatic hernia[8]
Crossed	Rare—approximately 1:7000	Across midline	See later section on abnormal fusion

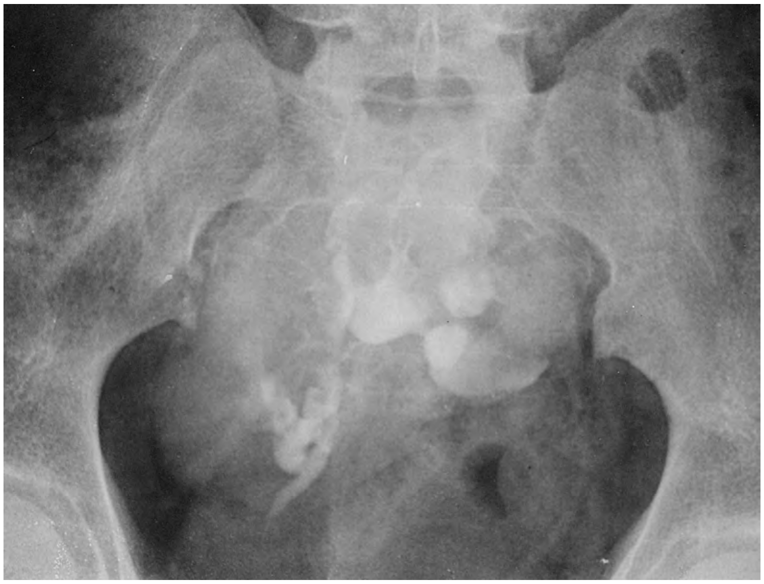

Figure 16-1 Pelvic kidney. Intravenous urography shows renal calyces of a kidney lying within the pelvis.

Table 16-2 Renal Ectopia: Associated Anomalies

Urinary	Contralateral renal agenesis
	Ectopic ureter
	Supernumerary kidney
	Retrocaval ureter
Genital	Female (75%)
	Bicornuate, unicornuate, or absent uterus
	Duplicate or rudimentary vagina
	Mayer-Rokitansky
	Male (15%)
	Undescended testis (5%)
	Hypospadias (5-10%)
	Duplicate urethra
Cardiac	Various anomalies
Skeletal	Scoliosis
	Hemivertebrae
Adrenal	Rare
Others	Fanconi syndrome
	Conjoined twins

anticipated, although this may be less likely in girls.[12] Pyeloplasty for PUJ obstruction may be necessary, and this may require a transperitoneal approach, either open or laparoscopic depending on the precise position of the kidney.

Renal stones may be treated with extracorporeal shock wave lithotripsy and percutaneous nephrostolithotomy with good results. Access to a pelvic kidney for percutaneous nephrostolithotomy may be difficult, but there are reports of laparoscopic guidance to help with a transperitoneal approach.[13]

ABNORMAL FUSION

During ascent, if the two developing kidneys come into contact in the midline, a horseshoe kidney results. If the lower pole of one kidney comes into contact with the upper pole of the contralateral kidney, cross-fused renal ectopia may result.

HORSESHOE KIDNEY

Horseshoe kidney is the most common fusion abnormality. The reported incidence is 1:400 to 1:1800 with a male-to-female ratio of 2:1.[14,15] A genetic basis for the anomaly has been postulated.[16] Inherited defects such as cystic renal disease occur with the same incidence as in normal kidneys.

Anatomy

The kidneys are joined by an isthmus, which may be fibrotic, dysplastic, or normal renal parenchyma (Fig. 16-3). In 95% of cases, the isthmus links the lower poles, and in 5%, it links the upper poles. The position of the isthmus can vary. In 40%, the isthmus lies at the L4 level, just below the origin of the inferior mesenteric artery, which passes over the isthmus. The presence of the inferior mesenteric artery may restrict ascent of the horseshoe during early embryogenesis. In another 40% of cases, the kidneys are united in a normal anatomic position, whereas in 20%, the kidneys lie lower in the pelvis.

The blood supply to horseshoe kidneys varies and has implications for surgery. Only 30% have a normal anatomic pattern. In the remaining 70%, the horseshoe is supplied by a combination of vessels entering from the aorta or the renal, mesenteric, iliac, or sacral arteries. The isthmus frequently has separate blood vessels that may occasionally represent the entire renal blood supply.[17]

Diagnosis

The diagnosis is usually made during routine investigations of the urinary tract. Ultrasound may show the abnormality of position and the connecting isthmus. Isotope studies usually

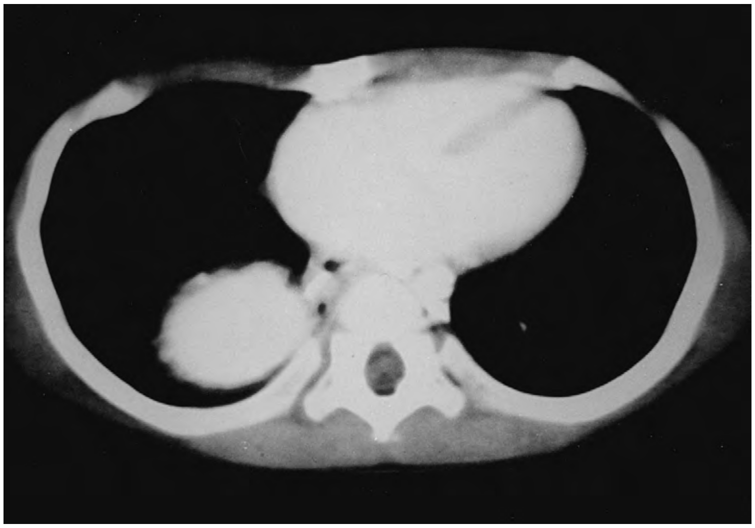

Figure 16-2 Thoracic kidney. CT scan (with intravenous contrast agent) shows the right kidney lying within the thoracic cavity.

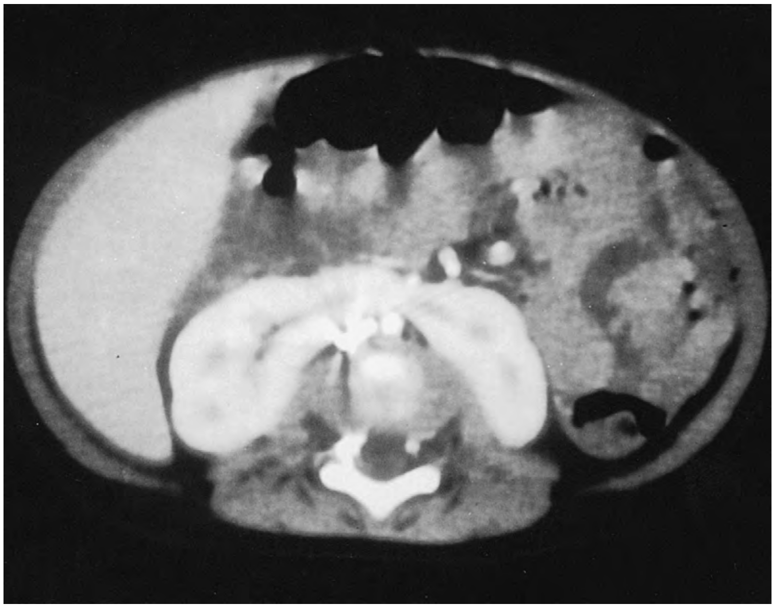

Figure 16-3 Horseshoe kidney. CT scan (with intravenous contrast agent) shows renal tissue with an isthmus crossing the midline.

reveal a functioning isthmus (Fig. 16-4). Intravenous urographic appearances are often classic with renal malrotation and medially pointing lower pole calyces. The upper ureters are often displaced laterally by the parenchymal bridge. Vesicoureteric reflux has been reported in 80% of cases,[18] with 30% overall having recurrent urinary tract infection. Micturating cystogram may suggest the diagnosis. Gadolinium-enhanced MR urography can show excellent anatomic information (Fig. 16-5).

Associated Abnormalities

Associated cardiovascular, genitourinary, skeletal, and neurologic abnormalities are reported in approximately 80% of cases.[19] There is an increased incidence of horseshoe kidney in trisomy 18 (20%) and Turner syndrome (7%). Later in life, there is an association with abdominal aortic aneurysms.[20]

Outcomes

Horseshoe kidneys are often asymptomatic,[21] and outcomes depend on associated urologic problems. Xanthogranulomatous pyelonephritis has rarely been reported.[22]

PUJ obstruction, more often left-sided, is the most common indication for surgical intervention. This obstruction may arise as a result of an intrinsic PUJ problem, impaired drainage secondary to the isthmus, or occasionally crossing vessels.[23] Depending on the position of the horseshoe, the PUJ may be approached retroperitoneally, either anteriorly or through the flank. A transperitoneal approach is occasionally necessary, and this has now been described using laparoscopic techniques. It is no longer considered necessary to divide the isthmus.[4] Good results have been reported using ureterocalicostomy for reconstruction, rather than a routine pyeloplasty, allowing dependent drainage.[24]

Renal calculi can be seen in 20% of cases. Extracorporeal shock wave lithotripsy may be used with similar success rates

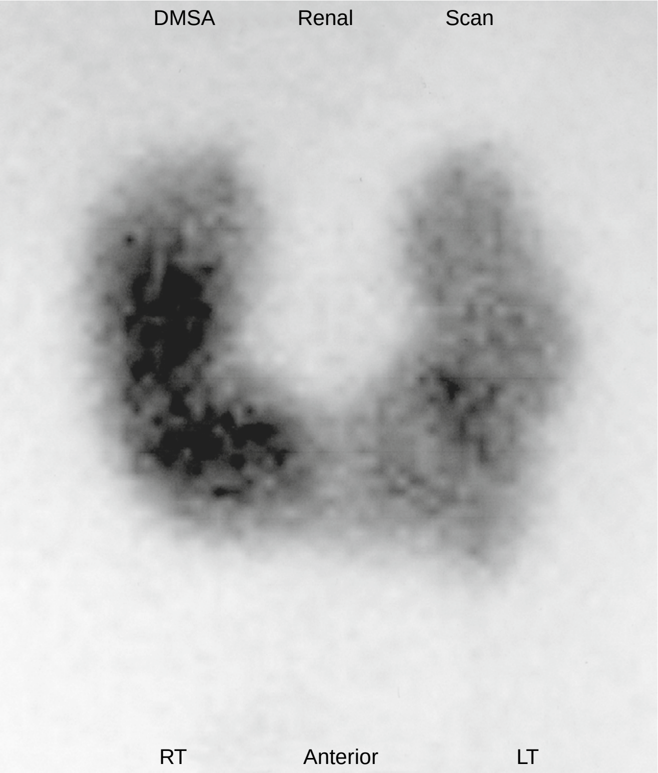

Figure 16-4 Horseshoe kidney. Tc 99m DMSA isotope scan shows functioning tissue in isthmus.

when used in normal kidneys. Although access for percutaneous nephrostolithotomy can be more difficult, stone clearance rates of 86% have been achieved in horseshoes, mainly using upper pole access.[25]

There seems to be an increased risk of malignancy in fused kidneys in childhood. Wilms' tumor occurs with a 1.5-fold to 8-fold increased risk, and can be difficult to diagnose and treat surgically.[26-28] In adult life, the risk seems less clear. Some reports suggest an increased risk of transitional cell carcinoma[29] and carcinoid tumors.[30] In a more recent review of the literature, Stimac and colleagues[31] found less than 200 cases of malignancy in horseshoe kidney and 4 cases in crossed fused renal ectopia. Renal cell carcinoma, transitional cell carcinoma, and oncocytoma all have been described, but the overall incidence of malignancy is probably no greater than in the normal population, although the diagnosis may be made relatively late.

CROSSED RENAL ECTOPIA

Crossed renal ectopia is the second most common fusion anomaly, occurring in 1:7000 with a male-to-female ratio of 2:1.[32] The left kidney is three times more likely to migrate to the right than vice versa. Crossed ectopia may occur with (85%) or without fusion (<10%), or, extremely rarely, may be solitary or bilateral (Fig. 16-6).[33-35] Other fusions, including lump kidney and L-shaped kidney, are extremely rare.

Anatomy

If fusion occurs, the upper pole of the crossed kidney fuses to the lower pole of the normally positioned kidney. The kidney usually remains incompletely rotated with the pelvis anterior.

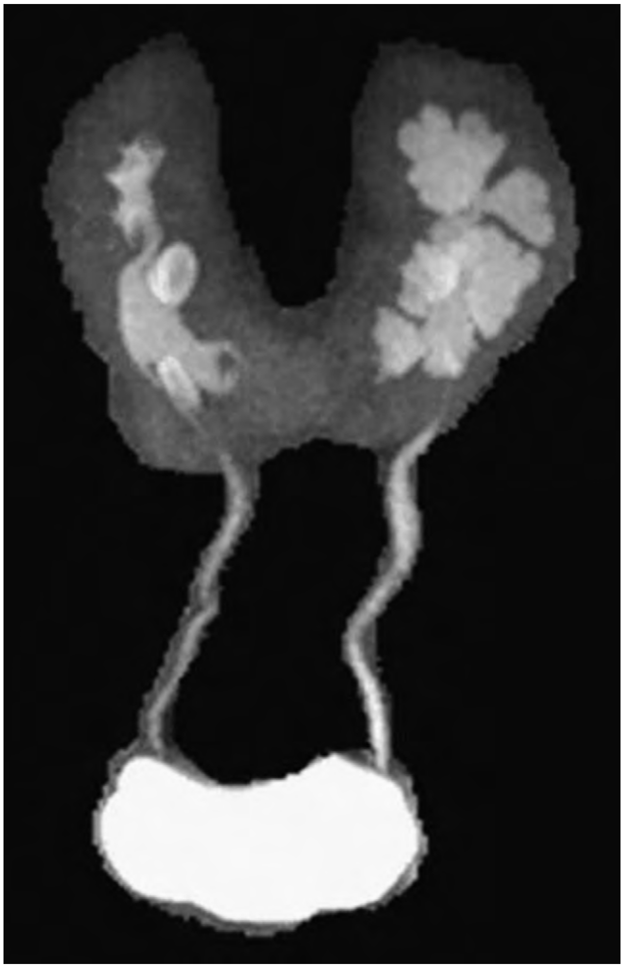

Figure 16-5 Horseshoe kidney. Gadolinium-enhanced MR urography shows excellent anatomic detail in uncomplicated horseshoe kidney. (Courtesy of Andrew Kirsch, Clinical Professor of Urology, Atlanta, GA.)

If complete rotation occurs before fusion, the pelves face in opposite directions, and this is known as an S-shaped or sigmoid kidney.

The blood supply of fused kidneys is extremely variable and may cross the midline. Urinary drainage is usually by separate ureters entering the bladder on either side of the trigone. Retroperitoneal masses and severe hydronephrosis may displace the kidney, giving rise to pseudoectopia.[36]

Diagnosis

Most fused kidneys remain undetected; when fused kidneys are detected, it is because of pyelonephritis (60%), loin mass (33%), or incidental discovery (7%) on routine screening for urinary abnormalities.[37] CT or MR urography may allow better definition of the exact anatomic picture (Fig. 16-7).

Associated Abnormalities

There is a high incidence of associated malformations, particularly if there is only one ureter. Malformations of cardiac, musculoskeletal, genital, gastrointestinal, anorectal, and renal systems are reported, occasionally as part of the VACTERL (*v*ertebral, *a*nal, cardiac, *t*racheal, *e*sophageal, *r*enal, and *l*imb) association.

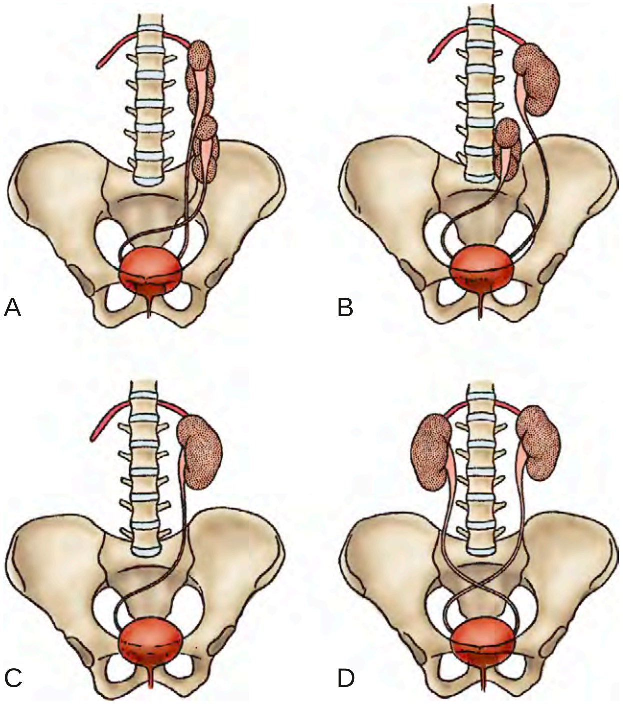

Figure 16-6 Crossed renal ectopia. **A,** Cross-fused ectopia. **B,** Cross-unfused ectopia. **C,** Unilateral crossed ectopia. **D,** Bilateral crossed ectopia. (**A-D,** From Ritchey M. Anomalies of the kidney. In: Kelalis PP, King LR, Belman AB, eds. *Clinical Pediatric Urology.* 3rd ed. Philadelphia: Saunders; 1992.)

CONCLUSION

Anomalies of kidney position and fusion are rare. Most of these anomalies remain asymptomatic throughout life. For patients affected by imperfect drainage, recurrent infection, or urolithiasis, renal function rather than position should dictate management.

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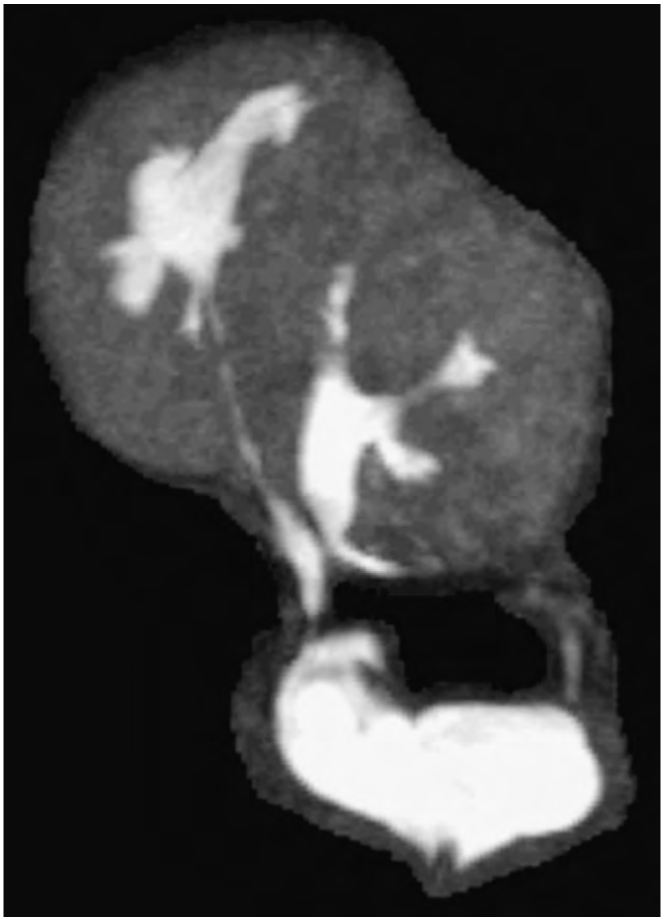

Figure 16-7 Gadolinium-enhanced MR urography of crossed fused renal ectopia. (Courtesy of Andrew Kirsch, Clinical Professor of Urology, Atlanta, GA.)

CHAPTER 17

MULTICYSTIC DYSPLASTIC KIDNEY DISEASE

Kristin A. Kozakowski, Sovrin M. Shah, and Kenneth I. Glassberg

In 1936, Schwartz[1] was the first to describe a "unilateral multicystic kidney" in a specimen removed from a 7-month-old boy suspected to have Wilms' tumor or massive hydronephrosis. He described an irregular lobulated mass with various-sized cysts resembling a "bunch of grapes." In 1955, Spence[2] observed that the prognosis of this condition was different from that of other cystic diseases of the kidney, particularly polycystic kidney disease. He noted the confusion in distinguishing cystic diseases of the kidney and called for the end of the "loose use" of the terms *polycystic, multicystic, multilocular,* and *multiple simple.* Subsequently, in 1964, Pathak and Williams[3] added the descriptive term *dysplastic* to these lesions, citing the presence of embryonic mesenchyme and primitive renal components (cartilage and muscle). This was based on previous reports that loose embryonic mesenchyme and cartilage were evidence of dysplasia.[4] The advent of routine antenatal screening ultrasonography led to a greater number of suspected multicystic dysplastic kidneys (MCDKs).

In an effort to consolidate the data and study the natural history and prognosis of this previously obscure disease, the American Academy of Pediatrics (AAP) Section on Urology established the Multicystic Kidney Registry in 1986. In 1987, the AAP Section on Urology Committee on Terminology, Nomenclature, and Classification set forth guidelines to clarify terms used to describe cystic renal diseases. *Dysplasia* is a histologic diagnosis based on the presence of primitive ducts and metaplastic cartilage. It can occur in varied amounts ranging from occupying isolated areas to encompassing the entire kidney. Dysplasia accompanied by cysts is referred to as *multicystic dysplasia,* whereas dysplasia with a preponderance of cysts encompassing the kidney is known as *multicystic dysplastic kidney*.

The morphologic appearance of an MCDK varies depending on the predominance or absence of the cystic component. Three morphologic types of MCDK exist. A kidney with small cysts and abundant dysplastic stroma is a solid cystic dysplastic kidney. A kidney with large cysts and minimal stroma is the typical MCDK. Finally, an identifiable renal pelvis within dysplasia is referred to as the hydronephrotic form of MCDK.[5]

Two phenotypes of dysplasia are associated with urinary tract abnormalities: obstructive and multicystic. Obstructive renal dysplasia associated with lower urinary tract obstruction is characterized by peripheral cortical cyst formation. In contrast, MCDKs are characterized by an absent or atretic pyelocalyceal system and multiple deformed cysts.[6] Shibata and colleagues[7] investigated the pathology of nine MCDKs using detailed morphologic analysis. They found that the incidence of glomerular cysts in MCDKs decreases with gestational age. Three-dimensional reconstruction also showed that the cysts were connected to the collecting ducts through tubules, and that basic nephron structures could be found in the cystic nephron. The three-dimensional analysis by Shibata and colleagues[7] supports a theory that cysts develop from early induced nephrons.

HISTOLOGY

Gross examination of a typical MCDK reveals multiple, variable sized cysts in a "bunch-of-grapes" type of cluster with very little intervening stroma, a loss of reniform configuration, and an absence of a calyceal collecting system (Fig. 17-1). The renal artery and vein are usually hypoplastic and sometimes absent.[8] The ureter may be absent, but is usually atretic. In cases of unilateral renal agenesis, this atretic ureter may be the only clue to a regressed MCDK. The cysts were previously thought to be noncommunicating. Felson and Cussen[5] reported communications to exist in histologic studies of MCDKs, however, an observation that has since been confirmed by several investigators.[9,10] Glassberg and Kassner[11] and Dewan and Goh[12] performed intracystic contrast injection studies to show the connections radiologically. Twenty of 22 MCDKs (including 5 with the hydronephrotic variant) reported in the literature were found to have connections between the cysts after undergoing intracystic contrast injection studies (Figs. 17-2 and 17-3). Glassberg and Kassner,[11] as had Griscom and associates[13] previously, found one or more pits (or orifices) at the hilar aspects of the cysts. These pits communicate with the tubular structures between the cysts.

Microscopically, the kidneys have features of abnormal metanephric differentiation. The AAP Section on Urology Committee on Terminology, Nomenclature, and Classification

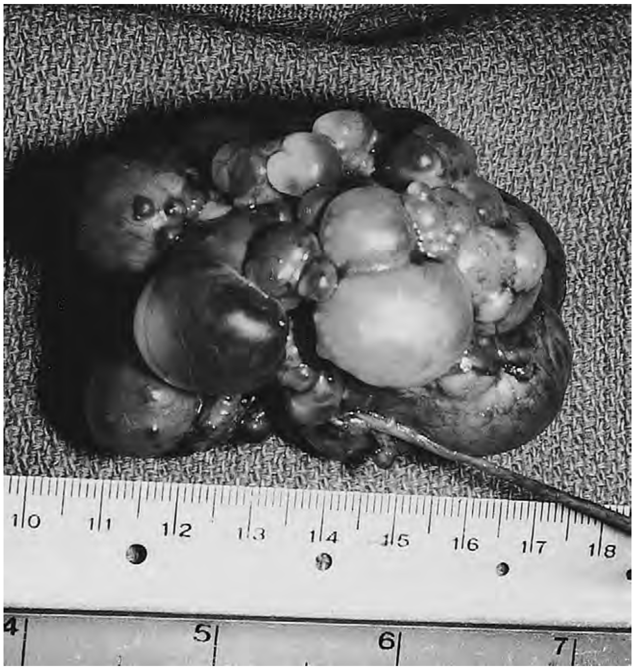

Figure 17-1 Typical multicystic dysplastic kidney appearing as a "bunch of grapes." The ureter was found to be narrow and atretic.

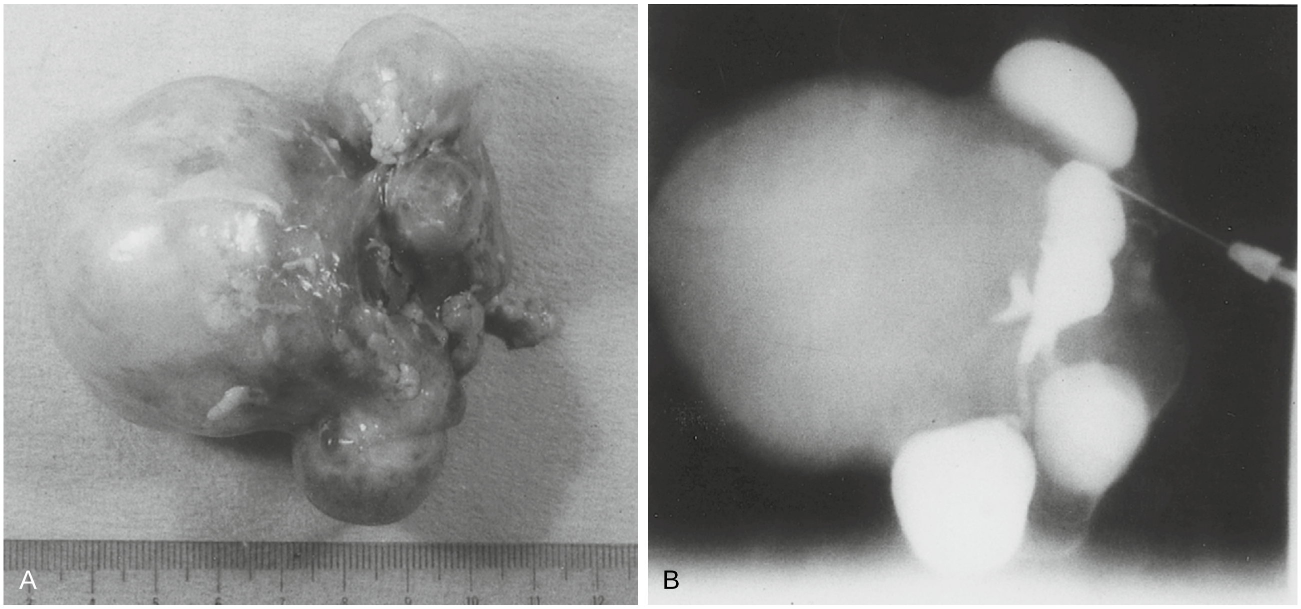

Figure 17-2 Hydronephrotic variant of a multicystic dysplastic kidney **(A),** with the corresponding intracystic contrast agent injection showing communication between cysts **(B).**

considered the presence of primitive ducts as evidence of dysplasia.[14] These ducts have concentric rings of connective tissue made of collagen, and occasional smooth muscle cells surround the primitive ducts.[2] Other findings include metaplastic cartilage, primitive tubules, glomeruli, and loose mesenchymal and fibrous tissue. Metaplastic cartilage may not be present in all cases, as shown by Matsell and colleagues,[15] who studied fetal MCDKs and were unable to show the presence of metaplastic cartilage. It may simply be that cartilage formation may not have occurred by the time the fetus died. In addition, metaplastic cartilage may resemble that found in the human kidney after an insult, as in neonatal renal necrosis and in scars after renal biopsy.[16,17] The presence of metaplastic cartilage may not rule in MCDK disease, but its absence does not rule it out.

In addition to dysplastic elements, components of normal nephrogenesis are found, including induced metanephric blastema and mesenchyme, S-shaped nephrons, maturing glomeruli with associated proximal and distal tubules, and ureteral duct.[15] The cysts are lined by flattened squamous to columnar-type epithelia that have been shown to originate from all segments of the nephron, including glomeruli, proximal tubule, and collecting duct.[15]

A large-scale autopsy study of 71 cases of MCDK confirmed the description of the kidney as a “bunch of grapes” with absent or atretic ureters.[18] Twelve of the contralateral kidneys showed associated abnormalities; four cases each had contralateral horseshoe kidney, ureteropelvic junction (UPJ) obstruction, and megaureters. They all displayed the hallmark of renal dysplasia: primitive ducts surrounded by a collar of immature mesenchyme, lobar disorganization, and abortive tubules and glomeruli. The primitive ducts predominantly comprise tall, columnar epithelium, followed by cases of cuboidal epithelium and a few cases of focal flattened ciliated columnar epithelium or squamous epithelium. The investigators also noted a thickened basement membrane in the primitive ducts in 64% of cases, which rendered it abnormally stretchable.

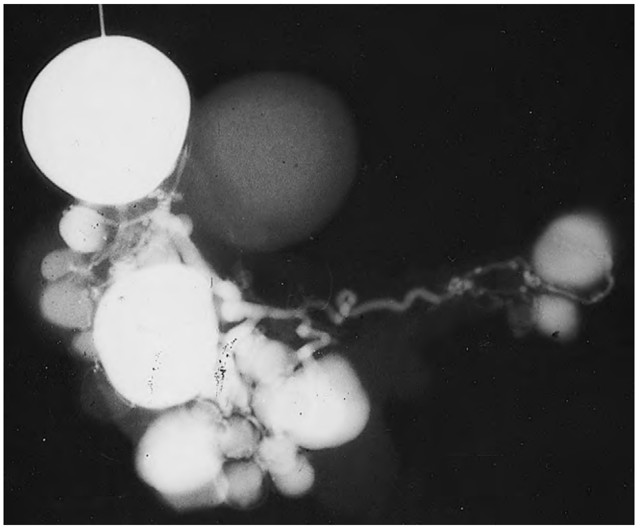

Figure 17-3 Contrast agent injection of a single cyst with subsequent imaging of many cysts. A connection is clearly seen between groups of cysts. (From Borer JG, Glassberg KI, Kassner EG, et al. Unilateral multicystic dysplasia in 1 component of a horseshoe kidney: case reports and review of the literature. *J Urol.* 1994;152[5 Pt 1]:1568-1571.)

ETIOLOGY

The etiology of MCDK disease is unclear. Many investigators have proposed that obstruction is the primary factor involved in the development of dysplasia.[17,19] Felson and Cussen[5] in 1975 viewed the multicystic kidney as an extreme form of hydronephrosis that occurs secondary to atresia of the ureter or renal pelvis. Cystic dysplasia of an entire upper pole can be seen in kidneys with duplicated collecting systems, especially associated with ureteroceles. Bilateral cystic dysplasia also may be seen secondary to posterior urethral valves. Animal models involving ligation of the ureter during early gestation have shown the induction of dysplasia.[19-22] Multicystic dysplasia secondary to obstruction has not been simulated in an animal model, however.

Shibata and Nagata[23] performed detailed morphologic studies of fetal dysplastic kidneys to show that early in utero obstruction causes urine retention in the developing nephrons, leading to multiple cyst formation. They reported that nephron induction with filtrating function occurs before the development of cysts; early fetal urinary tract obstruction causes cystic formation in the developing nephrons, which subsequently disrupts nephron induction and tubular development. Shibata and Nagata[23] also cited the importance of further investigation into abnormalities in the activity of transcription factor PAX2 and antiapoptosis protein BCL2 in the pathogenesis of renal dysplasia.[24]

In contrast, Hildebrandt[25] attributed the frequent association of an MCDK with ureteral or renal pelvis atresia to failure of union of the ureteral bud and the metanephric blastema, and the subsequent abnormal induction of the metanephric blastema by the ureteral bud. Matsell and colleagues[15] have shown, however, that there is no complete block in union because areas of normal nephrogenesis with collecting ducts may be seen in MCDKs. They instead propose that it may be abnormalities in branching of the ureteral bud that are responsible for progressive local histopathologic changes. This proposal is supported by previous findings of abnormal metanephric development (i.e., dysplasia) with ectopic ureteral orifices (i.e., ureteral budding) reported by Mackie and Stephens.[26]

Osathanondh and Potter[27] proposed that an ampullary abnormality in which there is premature termination of ampullary divisions results in a decreased number of generations of tubules, with the last generation being cystic. These abnormal tubules fail to induce metanephric differentiation. The occasional normal or near-normal nephron is the result of a rare normal ampulla and collecting tubules.

More recently, Spencer and Maizel[28] discovered that alterations in epithelial (ureteral) and mesenchymal cells by inhibition of glycosylation of the extracellular matrix could induce dysplasia without obstruction. The results of these experiments with chick embryos support the theory that dysplasia is the result of a disruption in normal epithelial-mesenchymal interaction during the induction of renal tubules. The important extracellular matrix constituents include fibrous proteins (collagen and elastin) and adhesive glycoproteins (fibronectin and laminin) embedded in a gel of proteoglycans (syndecan). In normal nephrogenesis, there is loss of fibronectin and collagen types I and III, which are replaced by other constituents, mainly laminin and syndecan. This process occurs because of interaction between the ureteric bud and the metanephric mesenchyme. Any alteration in the normal interaction can result in dysplasia.

To support this theory further, Radotra and associates[29] from India published a study in 2004 that examined the immunohistochemical expressions of adhesive glycoproteins, laminin, and fibronectin in 25 autopsy specimens of renal dysplasia and normal age-matched control cases. This study found that compared with normal nephrogenesis, there was significantly less expression of laminin and more expression of fibronectin in the extracellular matrix of dysplastic kidneys.

More recent studies have focused on finding the genes involved with renal development whose abnormal expression is responsible for renal dysplasia. Various genes have been identified, including *BMP4*, *FOXC1*, *KAL*, *EYA1*, and *AGTR2*; mutations in these genes have been identified in ectopic budding of the ureter from the wolffian duct and the subsequent urogenital anomalies.[30] One of the most studied is *PAX2*, a member of the PAX gene family that encodes transcription factors crucial in embryogenesis. It is expressed in mesenchymal/epithelial conversion and branching morphogenesis during nephron formation, and is involved with eye, ear, and central nervous system development. Its persistent expression has been shown to cause epithelial proliferation and cyst formation, as seen notably in renal coloboma syndrome, an autosomal dominant disorder that involves ocular and renal malformation, commonly vesicoureteral reflux (VUR) and renal hypoplasia. *PAX2* also is abnormally expressed in patients with Wilms' tumor and renal cell carcinoma owing to its relationship to *WT1* expression, which may be the link between dysplastic kidneys and malignant conversion.

Winyard and associates[24] showed that the PAX2 protein and BCL2, an antiapoptosis protein, are abnormally expressed in MCDK, and proposed that cyst formation in dysplastic kidneys is caused by overexpression of PAX2 and ectopic expression of BCL2; MCDK is a result of aberrant temporal and spatial gene expression. A case report has been published that described a family with renal coloboma syndrome and a novel mutated *PAX2* gene with autosomal dominant inheritance whose phenotype showed MCDK, VUR, UPJ obstruction, and renal hypoplasia.[31]

Although the etiology of MCDK disease remains unclear, theories of intrarenal obstruction and failure of ureteral bud–metanephros interaction predominate. Future research is necessary to elucidate further the complex genetic events that are responsible for renal dysplasia and the specific events that lead to multicystic renal dysplasia.

CLINICAL FEATURES

MCDK disease is one of the most common causes of an abdominal mass in infants.[13,32-35] The incidence of MCDK disease is estimated to be 1:3100 to 1:4300,[36] a much higher number than was reported in the era before routine antenatal ultrasound. Previously, the diagnosis was most often made in infancy in the presence of a palpable abdominal mass, which is found in 22% to 37% of cases.[35-37] It is difficult to ascertain what percentage of prenatally diagnosed MCDKs would have been identified by palpation during routine neonatal examination had the diagnosis not been made previously. Diagnosis may be made at 15 weeks of gestation on routine prenatal screening ultrasound; mean age of diagnosis is 28 weeks (range, 21 to 35 weeks).[38,39] MCDK is more common on the left, with a slightly greater incidence in boys.[33,40,41] Postnatal presentation includes palpable abdominal mass, flank pain, urinary tract infection (UTI), or hypertension. The October 2000 database of the AAP Multicystic Kidney Registry contains 903 patients (525 boys and 378 girls). The number of left-sided lesions was slightly higher than the number of right-sided lesions (471 left-sided lesions versus 417 right-sided lesions; 2 were bilateral, and 13 were not stated); 685 were diagnosed by antenatal ultrasound, and 103 were detected as a flank abdominal mass.[42] Most cases of MCDK are sporadic, although there have been case reports of families who exhibit an autosomal dominant inheritance pattern of MCDK.[43]

Autopsy study of prenatally detected bilateral MCDKs reported a frequency of 19% to 34%.[36,44,45] Reports from case series of bilateral postnatal MCDKs indicate an incidence of 2% to 8%.[46,47] This condition is incompatible with life, and infants affected usually have other syndromal congenital malformations, including Potter syndrome, Turner syndrome, Alagille syndrome, Waardenburg syndrome type I, Goldenhar syndrome, DiGeorge syndrome, Joubert syndrome, trisomy X, and Meckel syndrome.[48-56]

Renal agenesis and MCDK disease share similar clinical features, including male predominance, left-sided predominance, and a similar incidence of contralateral renal anomalies.[32] Hitchcock and Burge[57] reported nine cases of unilateral renal agenesis, of which seven had prenatal findings suspicious for MCDK disease. Mesrobian and associates[58] reported complete in utero regression of an MCDK, suggesting that some cases of unilateral renal agenesis may be a regressed MCDK. A blind-ending ureter in patients with unilateral renal agenesis may be a remnant of a regressed MCDK. Renal agenesis and MCDK disease may be part of a spectrum of a single disease process, which may affect one or both kidneys. Kleiner and coworkers[44] and Dungan and colleagues[45] reported an 11% and 14% incidence of renal agenesis contralateral to an MCDK. Most of these cases result in elective termination of pregnancy or early postnatal demise.

Segmental multicystic dysplasia may appear in horseshoe kidneys[59-61] and in single moieties of kidneys with duplicated collecting systems.[62] Borer and associates[61] reviewed the literature and found 18 cases with MCDK disease as a component of a horseshoe kidney. Laterality of the diseased segment was reported in 12, with equal occurrence in the right and the left kidneys. Segmental disease in a horseshoe kidney may present as a midline abdominal mass. A review of the literature by Corrales and Elder[62] found segmental MCDKs in a duplicated system to be more common in girls, with the left side involved more often than the right. Renal scintigraphy is essential in evaluation because ultrasound evaluation can overlook a functional segment that is obscured by the large cystic dysplastic portion. Anomalies in the lower, nondysplastic moiety include lower pole VUR, lower pole UPJ obstruction, and orthotopic ureterocele.

In 20% to 43% of MCDKs, contralateral upper or lower urinary tract abnormalities are encountered, with the most common being contralateral VUR, occurring in 15% to 28% of cases.[36-39,46,53-73] The 1993 report of the Multicystic Kidney Registry identified a 43% incidence of contralateral VUR; however, only 15% of patients had a voiding cystourethrogram (VCUG), so the overall rate of VUR was likely lower. In a long-term follow-up study of a regional multicystic kidney database of 202 patients, Aslam and Watson[63] reported a contralateral VUR rate of 19%; VCUG was performed in only 143 patients. Of patients, 74% had mild reflux (grade I-II), 22% had moderate reflux (grade III), and 2% had severe reflux (grade IV-V). The incidence of UTI was similar to patients who had no documented VUR, and no patients in the registry had renal scarring on any follow-up studies.[63] Another study of 75 patients with MCDKs showed a contralateral VUR rate of 26.4%, with most having grade I-II reflux that spontaneously resolved.[64] These data suggest that contralateral low-grade reflux associated with MCDK disease, treated with antibiotic prophylaxis, may have a similar incidence of spontaneous resolution as in patients without MCDK disease. The presence of a solitary kidney may warrant closer follow-up, however, in patients with MCDK and contralateral VUR.

Contralateral UPJ obstruction is found in 3% to 12% of patients.[66,70] Robson and Leung[32] suggested that MCDK disease is one in a spectrum of obstructing diseases that includes renal agenesis, MCDK disease, and UPJ obstruction. In such a spectrum, UPJ obstruction associated with an MCDK may be a bilateral obstructive process in which one side is more severely affected than the other. UPJ obstruction, similar to an MCDK, occurs more often in the left kidney and in boys.[71] Ureterovesical junction obstruction occurs in 4% to 6%[46,66,70] in addition to sporadic cases of ectopic ureters and ipsilateral obstructing ureteroceles.[69,72,73] The occurrence of crossed ectopic MCDKs also has been reported in the literature.[74]

In addition to anomalies of the contralateral kidney, patients with MCDKs can have malformations of the ipsilateral internal genitalia owing to the close embryologic relationship of the urinary and reproductive systems. Ipsilateral anomalies of the testes and vas may be associated with renal anomalies, including MCDKs, owing to their embryologic association with the wolffian duct. During development, the rete testes become continuous with the vas deferens and the epididymis, which are distal derivatives of the wolffian duct. The wolffian duct gives rise proximally to the ureteral bud, which induces the metanephros to form the kidney.

Insult to the wolffian duct can potentially cause renal and testicular defects. The most common abnormality of the wolffian duct is an absence of the vas deferens and ipsilateral renal agenesis.[75] Wolffian duct anomalies associated with MCDK disease include absence or ectopia of the ipsilateral vas deferens and cystic dysplasia of the testis.[76-81] Domini and associates[77] reported two very unusual cases in which an ectopic vas was connected to the ipsilateral MCDK via a common "ureterodeferential" duct that was proved to be vas deferens by histologic examination. Cystic dysplasia of the testes is a rare benign congenital cystic lesion of the rete testes and epididymal ducts. It is found at the mediastinum testis and may be seen ipsilateral to an MCDK or renal agenesis.[78-81] In a retrospective study of 93 patients, Merrot and coworkers[82] found that 15.1% had ipsilateral genitourinary abnormalities, which included seminal cysts, Gartner cysts, blind hemivagina, and VUR into seminal structures. These abnormalities persisted despite treatment or involution of the MCDK, and the authors stressed the need to follow these patients until puberty because the abnormalities can enlarge and become symptomatic.[82]

In other situations in which patients are left with solitary kidneys, the remaining kidney undergoes compensatory hypertrophy. In infants and children, this growth occurs in addition to the rapid growth and changes associated with normal renal maturation. Compensatory hypertrophy of the contralateral kidney has been reported in multiple series of patients with MCDKs. In the long-term study by Aslam and Watson,[63] 81% of the contralateral kidneys showed compensatory hypertrophy. In a large-scale Brazilian series of conservatively managed MCDK patients, 77% of the contralateral kidneys showed compensatory hypertrophy.[83] In MCDK, there is concern about the adequacy of renal growth in the contralateral kidney because of the increased incidence of abnormalities in these solitary kidneys. Shortliffe and colleagues[84] examined ultrasound scans from 48 patients with MCDK between 1988-2000 to construct a renal parenchymal area growth curve for the contralateral kidney and compare them with nomograms of normal kidney growth. These investigators found that only 9 of 48 contralateral kidneys showed subnormal compensatory growth; 4 of these patients had a renal abnormality in the solitary kidney. Longer follow-up studies are needed, however, to correlate the degree of compensatory hypertrophy with the eventual adult functioning of the contralateral kidney.

EVALUATION

Most MCDKs are detected early in the antenatal period because of routine use of fetal ultrasound. Abdominal masses in neonates, infants, and children are most commonly of urologic origin, most likely hydronephrosis or MCDKs.[85,86] Gloor and colleagues[87] showed that greater than 50% of infants with an antenatal diagnosis of urinary tract abnormalities had either hydronephrosis or MCDKs. Distinguishing hydronephrosis from MCDK disease is essential because the approach to therapy and indications for surgery differ in each. If not detected on antenatal ultrasound, an MCDK may manifest in infancy or childhood as abdominal fullness or an abdominal mass. It may be discovered later in life during an evaluation for UTI, hematuria, hypertension, or other concurrent congenital or genitourinary abnormality.

Ultrasound in combination with renal scintigraphy yields an accurate diagnosis of MCDK disease in 93% of suspected cases.[88] In the rest, confusion lies in distinguishing hydronephrosis from a cystic dysplastic kidney with a single predominant cyst. Postnatal ultrasound evaluation of the kidneys should be performed to confirm the prenatal findings. Generally, there is a loss of a normal reniform configuration with minimal, if any, parenchyma and cysts of varied sizes that are haphazardly arranged without a distinct larger central or medial cyst. A central medial cyst suggests the presence of a renal pelvis and could represent either the hydronephrotic form of MCDK disease or UPJ obstruction. When there is an identifiable renal sinus, the diagnosis is more likely hydronephrosis. Stuck and coworkers[88] have characterized ultrasound features of MCDK disease: the presence of sharp interfaces between multiple, randomly arranged, and variably sized cysts, the largest cyst with nonmedial location; a lack of an identifiable renal sinus; and an absence of renal parenchyma.[38,88]

Suspicious ultrasound findings should be correlated with renal scintigraphy findings of the absence of renal function. Occasionally, renal scintigraphy may show a functional segment associated with an MCDK in a duplicated system.[65] Ultrasound may obscure the normal parenchyma because of the overgrowth of the multicystic dysplastic segment. Parenchymal imaging agents such as Tc 99m DMSA have traditionally been used. This agent is absorbed and retained by proximal tubular cells, providing an excellent picture of functional parenchyma or defects indicating nonfunctioning parenchyma. Because the Tc 99m DMSA label is retained and not excreted, the inability to assess the excretory phase of renal function makes it impossible for Tc 99m DMSA to distinguish accurately an MCDK from hydronephrosis caused by UPJ obstruction.[89,90] If Tc 99m DMSA shows nearly complete or complete absence of function, the diagnosis is much more likely to be an MCDK rather than UPJ obstruction. Keep in mind that MAG3 is an excellent agent to evaluate function, in particular when evaluating for obstruction with a furosemide renogram and when function is thought to be present, but in general Tc 99m DMSA is the agent of choice when trying to identify if any functional tissue is present at all.[91,92] Aggressive evaluation and treatment of the only functioning kidney are vital.

Traditionally, complete evaluation of an MCDK has also included a VCUG. Contralateral VUR has been reported to be associated with an MCDK in 15% to 28% of cases in the literature.[36,63,66-69] Early detection of contralateral VUR is important in the prevention of pyelonephritic scarring and deterioration of renal function in the only functioning renal unit.[67] Blane and associates[93] reported that ultrasound alone cannot be relied on to screen selectively for VUR based on their study that found normal ultrasound findings in 74% of refluxing units. Ismaili and associates[94] challenge routine VCUG, however, and assert that VCUG is unnecessary as routine screening in patients with MCDK. In their study of 76 newborns with antenatally detected MCDK, Ismaili and associates[94] found that two successive normal neonatal renal ultrasound scans can rule out any clinically significant contralateral anomalies, making VCUGs unnecessary. Only four (7%) of the infants with two normal renal ultrasound scans had contralateral VUR; all were grade I-II and resolved spontaneously by age 2.

Siegel and Feldenberg[95] evaluated the clinical course of 35 patients with MCDKs to predict which patients were at greatest risk for significant damage to the contralateral solitary kidney independent of the results of a VCUG. The patients were divided into simple MCDK (no associated genitourinary anomalies) and complex MCDK (bilateral dysplasia or associated genitourinary anomalies not including VUR). In the simple MCDK group, all patients had an excellent clinical outcome with no damage to the contralateral kidney. Presence or absence of VUR was not a predictor of UTI. In the complex MCDK group, the patients had a higher rate of contralateral kidney damage; however, associated structural genitourinary anomalies were stronger predictors of prognosis than the presence or absence of UTI or VUR.

Fetal renal artery Doppler studies have been investigated to determine if postnatal renal function can be predicted in morphologically abnormal prenatal kidneys. Gill and colleagues[96] studied renal artery Doppler waveforms of five fetuses suspected to have unilateral MCDK disease with the contralateral kidney of each serving as control. Renal artery flow was absent in the suspected moieties, but present in the contralateral unaffected moieties. Postnatal scintigraphy was used to confirm nonfunction in the cystic kidneys. One kidney, with a duplex system, had a cystic upper moiety and a hydronephrotic noncystic lower moiety. Doppler waveforms were detected in the lower, but not in the upper, segment. Postnatal evaluation with duplex Doppler studies of the renal artery and vein also showed abnormal waveforms. Duplex Doppler ultrasound may serve as an adjunct in diagnosing MCDK disease and perhaps may replace postnatal renal scintigraphy.[96]

The diagnosis of an MCDK is suspected on renal ultrasound (loss of reniform configuration, multiple cysts, nonmedial location of largest cyst, absent pelvis, minimal to absent renal parenchyma) and confirmed by renal scintigraphy (lack of function). Postnatal imaging of the contralateral kidney with ultrasound is important to detect abnormalities; however, it remains controversial as to whether routine VCUG is necessary if the renal ultrasound scan is normal.

NATURAL HISTORY

Long-term data are now available for several large studies of patients with MCDK. These data have provided information about the natural history of the disease.

Infection

There has been no definitive correlation between MCDK and increased risk of UTI. The concern for increased incidence of infection is mainly due to the higher rate of abnormalities in the contralateral kidney.

In the study by Aslam and Watson[63] of 202 patients with MCDKs, 20 patients had UTIs; none required hospitalization or parenteral antibiotics, and no patients developed renal scarring. Only seven of these patients had documented VUR. In another series of 43 patients with MCDKs managed conservatively, only 4 patients had UTIs, and no patients had contralateral renal scarring.[83]

Hypertension

Hypertension has been reported in patients with MCDK, and the risk of hypertension has often prompted parents to choose nephrectomy over conservative management. Studies have suggested that the mechanism of hypertension is ischemia-induced renin secretion in the juxtaglomerular apparatus of mature glomeruli and interlobular arteries in the scarred areas of the dysplastic kidney.[97] In a large-scale review of the literature, Narchi[98] analyzed 29 studies of patients with MCDKs and found that only 6 of the 1115 children developed hypertension; the probability of a child with unilateral MCDKs developing hypertension is 5.4 per 1000 (95% confidence interval 1.93 to 11.7 per 1000), which is similar to the risk in the general pediatric population.[99] Critics point out that there was no uniform definition of hypertension and minimal long-term follow-up of most of the patients; there have also been several studies that showed a subtle increase in blood pressure in children with a solitary kidney from other causes.[100] In the Aslam and Watson[63] study, however, after 10 years of follow-up, there was still no child who developed hypertension. A survey of physicians reported that 15% have treated hypertension related to MCDKs,[101] suggesting that hypertension associated with MCDKs may be underreported,[102] perhaps because of the previous lack of antenatal screening with ultrasound.

The literature on surgical causes of hypertension does not report MCDKs as a significant cause of pediatric hypertension.[103,104] Numerous small series have shown resolution of hypertension after nephrectomy.[105-109] Webb and coworkers[109] noted poorer rates of resolution of hypertension after nephrectomy with increasing age, possibly resulting from hypertension-induced damage of the contralateral, originally healthy arteriole. Cases of hypertension associated with MCDKs and cured by nephrectomy are reported in the literature. The true risk of hypertension cannot be assessed, however, given sporadic case reports. Routine surgical treatment of MCDKs based on the risk of hypertension cannot be substantiated, but when hypertension is diagnosed in a child with an MCDK, prompt surgical excision is recommended to ensure the best chance of cure.

Malignancy

In a review of the literature, Perez and associates[70] found multiple reports of malignancy arising in MCDKs, including renal cell carcinoma (5 cases),[110-114] malignant mesothelioma (1 case),[115] and Wilms' tumor (11 cases).[6,116-122] Renal cell carcinoma is common, with 25,000 new cases reported each year.[58] This fact, in conjunction with Beckwith's[119] observation that renal cell carcinoma may be difficult to distinguish from multicystic renal carcinoma, makes one question whether there is truly an increased risk above that of the normal population.

Wilms' tumor has a more solid association with MCDKs, as shown by Perez and associates[70] in a thorough review. The dilemma arises in ascertaining the frequency with which Wilms' tumor arises in MCDKs. Noe and Raghavaiah[123] used a 5% incidence of nodular renal blastema in MCDKs and a 1% incidence of Wilms' tumor from nodular renal blastema[124] to calculate a 0.05% risk of Wilms' tumor in MCDK disease. This finding was corroborated by Perez and associates,[70] who used the risk of Wilms' tumor, risk of MCDKs, and yearly birth rate to estimate the risk of Wilms' tumor arising in MCDKs to be 3:10,000 to 10:10,000 (0.03% to 0.1%). They estimated two to eight new cases of Wilms' tumor in children with MCDKs each year if there are 6000 to 8000 children with MCDKs in a given year. In a 30-year review, however, only six such cases in the United States have been reported, suggesting the true risk of Wilms' tumor in children with MCDKs should be significantly lower than the calculated rate of 0.03% to 0.1%.[70]

Beckwith[125] reported no increased risk of Wilms' tumor in dysplastic kidneys in his experience. According to a more recent review of the Multicystic Kidney Registry, two cases of Wilms' tumor have occurred among 608 nonoperative cases.[42] Narchi[126] performed a systematic review of the literature, and in 26 studies of 1041 children with unilateral MCDKs managed conservatively, no children developed a Wilms' tumor. Narchi[126] also pointed out that because Wilms' tumors grow quickly, ultrasound scans at intervals less than every 3 months would not help to decrease tumor stage at presentation. There is no evidence to support following these patients with routine ultrasound scans if the contralateral kidney is normal.

Another argument favoring the association between Wilms' tumor and MCDKs is the finding of nephrogenic rests, recognized as precursors to nephroblastoma, within an MCDK. The presence of multiple areas of nephrogenic rests is referred to as nephroblastomatosis. These rests may remain quiescent or become hyperplastic, forming a nodule (adenomatous focus or nodular renal blastema), possibly an early stage in tumor formation.[127] Not all cases of nodular renal blastema progress to Wilms' tumor, however, because nodular renal blastema is reported in 0.25% to 0.5% of normal kidneys,[124-128] and the actual rate of Wilms' tumor in the general pediatric population is significantly lower. Most nephrogenic rests along with MCDKs regress rather than undergo malignant degeneration.

Regression

Pedicelli and colleagues noted spontaneous regression in 809 MCDKs.[129] In a retrospective review, Rottenberg and colleagues[130] reported 55 cases, of which 40% (22) of the MCDKs regressed completely at a mean of 21 months, and 33% (18) decreased in size as shown by ultrasound evaluation. Kessler and associates[37] reported retrospectively on 14 of 23 (61%) patients with spontaneous regression at a mean of 10 months. A prospective study of the natural history of MCDK showed complete regression in 21% (7 of 33) and a decrease in size in 61% (20 of 33) at 24 months.[131] As of October 2000, the AAP Multicystic Dysplastic Kidney Registry had follow-up data on 622 patients at 1 to 3 years after diagnosis. Of these, 286 (46%) MCDKs were smaller, 26 (4.2%) were larger, 211 (33.9%) were unchanged, and 99 (15.9%) had disappeared completely.[42] At 10 years of follow-up, Aslam and Watson[63] showed that 33% had involuted at 2 years of age, 47% at 5 years, and 59% at 10 years (Figs. 17-4 and 17-5).

Prenatal regression also can occur and may be mistaken for unilateral renal agenesis.[35,45] Many have proposed a common embryologic insult resulting in differing degrees of malformations, ranging from renal agenesis to dysplastic kidney to MCDK disease.[32,57,58] Ashley and Mostofi[132] showed 19 of 157 cases of unilateral renal agenesis in the presence of an ipsilateral ureter, suggesting the former presence of a renal unit. The etiology of unilateral renal agenesis remains multifactorial, however.

Regression does not imply cure or eliminate the risk of morbidity associated with MCDK disease. Some studies have shown that the risk of hypertension and malignant degeneration is not eliminated with regression.[109,114] Gough and associates[133] reported on four patients with regression by ultrasound criteria who underwent exploration to remove any possible residual tissue according to the parents' wishes. All four patients were found to have substantial residual masses proved by histologic examination at the time of surgery. Involution is accomplished by progressive decompression of cystic fluid, leaving behind the thin, dysplastic parenchyma,[134,135] although Avni and colleagues[39] have reported the absence of tissue at exploration. In addition, there is no evidence that size predicts the risk of hypertension or malignant transformation.[35] Early ultrasound detection of malignant degeneration proves to be difficult in a small, involved kidney. Screening for UTI, microhematuria, and the urine cytologic appearance is unreliable in the presence of ureteral atresia that separates the kidney from the lower urinary tract.[6,35]

TREATMENT

Conservative management of MCDK disease is supported by the high rate of spontaneous regression and low rate of hypertension, UTI, and malignancy. The regimen for follow-up study is quite varied. Each visit should include a physical examination, evaluation of blood pressure, urinalysis, and a urine culture if needed. There is no consensus for the ideal interval of screening ultrasound. The study by Aslam and Watson[63] proposes that after 2 years, the next clinical and ultrasound follow-up should be at 5 years and then 10 years as long as no UTIs, abdominal complaints, failure to thrive, or headaches develop. Another study also proposed that yearly ultrasound follow-up is unnecessary, and that the routine follow-up examinations for hypertension, abdominal mass, and UTIs can be performed by the primary care physician. The additional ultrasound studies were a source of considerable parental anxiety.[135]

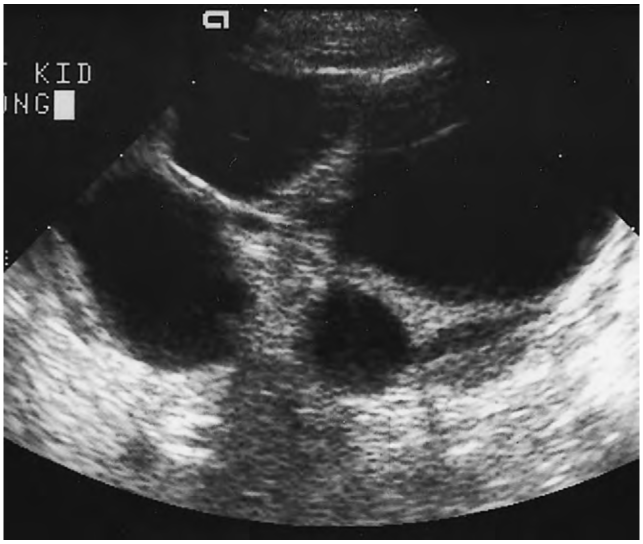

Figure 17-4 Postnatal ultrasound of a multicystic dysplastic kidney.

Al-Khaldi and associates[36] follow their patients with ultrasound at 2 and 5 years of age and blood pressure and urine cultures every 6 months. Oddone and colleagues[117] obtain renal ultrasound results every 3 months for 5 years. Wacksman and Phipps[42] suggest renal ultrasound every 3 to 6 months for the first year of age, every 6 to 12 months to 5 years of age, and every year thereafter because the risk of Wilms' tumor is decreased after 5 years of age. Given the rapid tumor doubling rate of 6 to 40 days, Perez and associates[70] suggest that screening ultrasound may be the most beneficial in early detection of Wilms' tumor formation if performed every 3 to 4 months to the age of 8 years. They concluded, however, that the morbidity of MCDK disease, although it exists, is low, and they do not advocate either screening ultrasound or nephrectomy.

Based on our review of the literature, conservative follow-up includes renal ultrasound every 3 to 4 months to age 3 years, every 6 months to age 5 years, and then every year to age 8 years.[136] This regimen would be costly when considered on a national level compared with early nephrectomy; however, it takes into account the following observations of Perez and associates[70]: (1) The development of Wilms' tumor in MCDK disease is earlier than in the general pediatric population with a mean age of 25 months compared with 3 to 4 years. (2) The oldest reported child with Wilms' tumor in an MCDK is 6.5 years. (3) In the general pediatric population, 95% of all Wilms' tumors develop before the age of 8 years.

In some cases, close, long-term follow-up with ultrasound and physical examination may be easier said than done, and rigid compliance may be unrealistic. In these cases, early surgical excision may be the best treatment. This approach is especially feasible given the ability to perform outpatient nephrectomy with minimal morbidity. Also, complications arising from the MCDK may necessitate early nephrectomy.

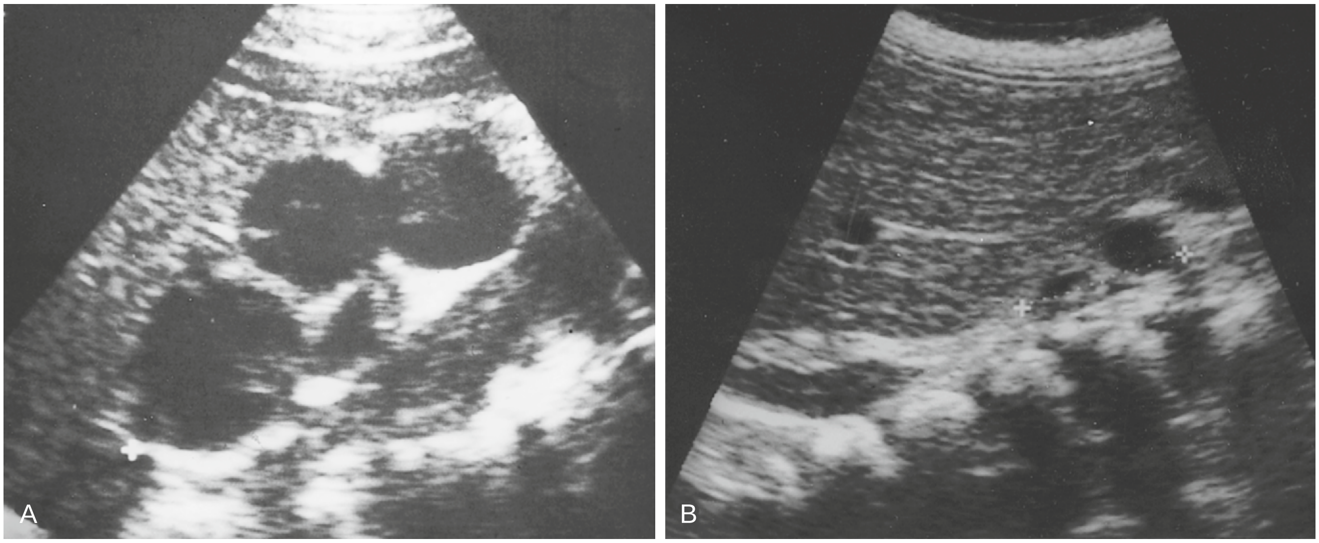

Figure 17-5 Ultrasound studies of a multicystic dysplastic kidney at birth (**A**) and at 9 months of age (**B**) show an almost completely regressed kidney.

Elder and coworkers[108] reported impressive results with outpatient nephrectomy through a small subcostal incision. Removal of the kidney is facilitated by decompression of the MCDK before removal.

Thirty cases were performed for MCDKs according to the parents' choice after long-term follow-up and nephrectomy was offered. All procedures were done on an outpatient basis except one, in which nephrectomy of an already decompressed kidney was difficult. The average operative time was 45.4 minutes. The advent of feasible laparoscopic nephrectomy in children has made early surgical treatment a more viable option. A study of 13 patients with MCDKs who underwent transperitoneal laparoscopic nephrectomy using three port sites showed minimal blood loss, no intraoperative complications, average anesthetic time of 86 minutes, and average hospital stay of 27 hours.[137] In carefully selected cases, early surgical intervention may offer the best treatment, avoid complications associated with MCDK disease, and obviate the need for lifelong follow-up.

The high rate of spontaneous regression and low rate of hypertension, UTI, and malignancy do not justify routine surgical excision, although the latter is cost-effective and offers immediate cure. The parents should be an integral part of the decision-making process. The risk of development of hypertension and malignant degeneration should be explained. The necessity of long-term follow-up should be emphasized. Surgical excision may be offered as an immediate means of cure, especially if outpatient nephrectomy or laparoscopy is available. Homsy and colleagues[122] suggested the formulation of an objective consent form outlining the risks and benefits of observation versus surgery to facilitate decision making.

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CHAPTER 18

GLOMERULONEPHRITIS IN CHILDREN

Sharon Phillips Andreoli

Glomerulonephritis (GN) is a common cause of acute kidney injury and chronic kidney disease in children. GN during childhood also may lead to chronic kidney disease or other complications that do not become apparent until adulthood. In addition, GN causes substantial morbidity, and therapy for glomerular diseases, including corticosteroids and immunosuppressive agents, contributes to side effects and morbidity. The chronic glomerulonephritides that lead to permanent loss of nephron mass may manifest with an acute nephritic syndrome, nephrotic syndrome, or asymptomatic hematuria or proteinuria or both.

Table 18-1 categorizes the common and uncommon glomerulonephritides that may occur in children. The natural history and long-term prognosis of the different forms of GN vary. Postinfectious GN has an excellent long-term prognosis, and Henoch-Schönlein purpura (HSP) leads to chronic kidney disease in less than 1% to 2% of unselected cases.[1-5] In contrast, untreated membranoproliferative glomerulonephritis (MPGN) eventually leads to chronic kidney disease in approximately 90% of cases, and rapidly progressive glomerulonephritis (RPGN) requires prompt diagnosis and therapy to preserve renal function.[4-8] The long-term prognosis of IgA nephropathy also varies, but it is estimated that 20% to 40% of children with IgA nephropathy have a chronic progressive course with eventual development of chronic kidney disease.[5,9,10]

Prompt diagnosis and initiation of specific therapy when indicated, and avoiding unnecessary therapy are important in managing a child with GN so that maximal renal function can be preserved, and side effects of therapy can be minimized. This chapter reviews the clinical manifestations, laboratory and pathologic features, pathophysiology, and potential treatment strategies for the common glomerulonephritides that occur in children.

HYPOCOMPLEMENTEMIC GLOMERULONEPHRITIDES

Serologic studies and complement levels are important in evaluating a child with clinical and laboratory findings suggestive of GN. The third component of complement (C3) is usually depressed in postinfectious GN, in MPGN, in GN associated with systemic lupus erythematosus (SLE), and in nephritis of chronic infection (see Table 18-1).[2,5,11] MPGN is divided further into three subtypes—type I; type II, also called dense deposit disease; and type III. Postinfectious GN and MPGN are primary renal diseases, whereas SLE and nephritis of chronic infection are systemic diseases that involve the kidney. C4 is usually depressed in type I and III MPGN and in lupus GN, suggesting that complement is activated by the classic pathway, whereas C4 is usually normal in type II MPGN and in postinfectious GN, suggesting that complement activation is via the alternative pathway in these diseases. The mechanism of complement activation and hypocomplementemia is complex and seems to be related to increased catabolism and decreased synthesis. In MPGN, increased degradation is associated with the presence of C3 nephritic factor in 30% to 75% of cases.[13] A low C3 is associated with active renal disease in postinfectious GN and in lupus nephritis, whereas the C3 level does not correlate with prognosis, disease activity, or progression of renal disease in MPGN.

Postinfectious Glomerulonephritis

Epidemiologic studies in siblings of children with confirmed postinfectious GN have shown that some have urinary abnormalities compatible with mild postinfectious GN.[13] Some children with postinfectious GN may be asymptomatic, but most who come to medical attention have an abrupt onset of an acute nephritic syndrome that includes hematuria, fluid retention, and hypertension with or without renal insufficiency. The typical child presents with an acute nephritic syndrome 7 to 21 days after an infection. Hematuria is gross in 30% to 50% of cases. The degree of hypertension varies; blood pressure may be only mildly elevated, or the presenting symptoms may be related to hypertensive encephalopathy in a few cases. Edema is usually due to fluid retention, rather than the nephrotic syndrome, and pulmonary congestion and cardiomegaly are common in postinfectious GN. Renal insufficiency is usually mild, but occasionally may be severe. Postinfectious GN typically occurs in children 2 to 12 years old.

In 80% to 90% of cases, postinfectious GN occurs after an infection with a nephritic strain of group A beta-hemolytic streptococcus; postinfectious GN is frequently called poststreptococcal GN. The preceding streptococcal infection is usually a pharyngeal or pyodermal skin infection. In a few cases, GN may follow viral, fungal, or other bacterial infections. Hematuria is seen in nearly all cases, and gross hematuria with tea-colored or cola-colored urine is common. The proteinuria may range from several hundred milligrams to a few grams per day, and the serum albumin is usually mildly depressed. Proteinuria sufficient to result in hypoalbuminemia and edema is rare, occurring in less than 10% of cases, and the edema in postinfectious GN is usually due to fluid retention, rather than hypoalbuminemia. The C3 is low in 85% to 95% of cases, and the Streptozyme test is positive when the preceding infection was a streptococcal infection.

An antistreptolysin O (ASO) titer and the Streptozyme test are the two tests commonly used to evaluate for previous streptococcal infection. The ASO titer measures antibodies only to streptolysin O and increases after a preceding pharyngeal infection, but there is a significantly blunted response when the preceding infection is pyodermal.[14-16] This is thought to be due to lipids and cholesterol esters in the skin interfering in antigen recognition of the streptolysin O antigen. The Streptozyme test detects antibodies to approximately five streptococcal antigens, including streptolysin O, hyaluronidase, DNAase B, NADase, and other less well-defined streptococcal antigens.[16] Each test is positive in approximately 16% to 18% of healthy children. Because of the high positive rate in healthy children, a positive Streptozyme test in a patient with hypocomplementemic GN does not confirm that the nephritis is truly poststreptococcal. Although a positive Streptozyme test supports a presumptive diagnosis of poststreptococcal GN, a negative Streptozyme test suggests an

Table 18-1 Classification of Glomerulonephritis in Children

- Hypocomplementemic glomerulonephritis
  - Postinfectious glomerulonephritis
  - Membranoproliferative glomerulonephritis
  - Systemic lupus erythematosus nephritis
  - Nephritis of chronic infection
- IgA-related glomerulonephritis
  - IgA nephropathy
  - Henoch-Schönlein purpura
  - Systemic lupus erythematosus nephritis
- Membranous glomerulonephritis
- Rapidly progressive glomerulonephritis
  - Postinfectious glomerulonephritis
  - Membranoproliferative glomerulonephritis
  - Systemic lupus erythematosus nephritis
  - Henoch-Schönlein purpura
  - ANCA-positive glomerulonephritis
    - Pauci-immune rapidly progressive glomerulonephritis
    - Wegener granulomatosis
    - Polyarteritis nodosa
  - Anti-GBM antibody disease
    - Goodpasture syndrome

ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane.

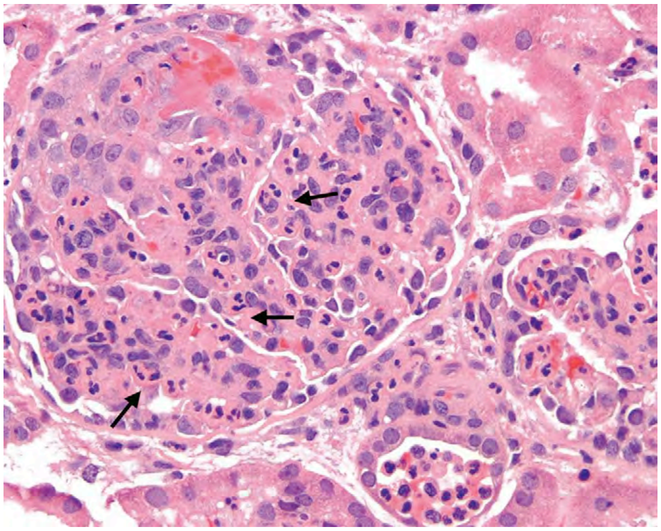

Figure 18-1 Light microscopy of kidney biopsy specimen from a 5-year-old boy with postinfectious glomerulonephritis. Periodic acid–Schiff stain shows diffuse endocapillary proliferation with segmental infiltration of polymorphonuclear leukocytes *(arrows)*.

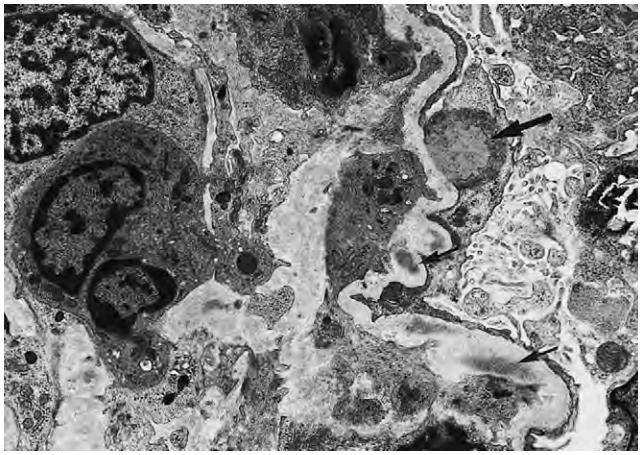

Figure 18-2 Electron microscopy of a glomerulus from the 5-year-old boy in Figure 18-1 with postinfectious glomerulonephritis shows a large subepithelial "hump" characteristic of poststreptococcal glomerulonephritis *(large arrow)* and smaller subepithelial deposits *(small arrows)*.

alternative diagnosis, or that the preceding infection was not a streptococcal infection.

Most children with a clinical course consistent with postinfectious GN do not need a kidney biopsy, but in atypical cases, or if there is rapid deterioration of renal function consistent with RPGN, a kidney biopsy may be necessary to make a definitive diagnosis.[1] Light microscopy in postinfectious GN typically reveals a diffuse proliferative GN characterized by proliferation of mesangial cells with an exudative inflammatory infiltrate consisting predominantly of polymorphonuclear leukocytes (Fig. 18-1). Crescents may be present, particularly if the child has a clinical course consistent with RPGN. Immunofluorescent studies show mesangial and glomerular basement membrane (GBM) deposition of IgG and C3. Other immunoglobulins and complement components may be present to a lesser degree. Electron microscopy shows mesangial and subepithelial electron-dense deposits in large "humps" that are characteristic of postinfectious GN (Fig. 18-2).

More recent studies show that some children may have a genetic predisposition to poststreptococcal GN; endothelial nitric oxide synthase gene intron 4 a/b VNTR polymorphisms were more common in children with poststreptococcal GN compared with control children.[15] In that study, specific polymorphisms also were associated with a more severe clinical course.[15] The pathogenetic mechanisms that cause postinfectious GN are unclear, but the acute onset of the disease after a streptococcal infection suggests that secreted products of the nephritogenic strains of streptococci may initiate the inflammatory process. Streptococcal pyogenic exotoxin B is an extracellular binding protein secreted by nephritogenic streptococci that has been preliminarily shown to activate complement.[16] Serologic and immunofluorescent studies have shown that sera from patients with poststreptococcal GN contain antibodies directed against the streptococcal pyogenic exotoxin B, and that a large percentage of kidney biopsy specimens from patients with poststreptococcal GN stained positive for streptococcal pyogenic exotoxin B.[16]

Other studies have shown the presence of streptococcal antigens including glyceraldehyde phosphate dehydrogenase (GAPHD), suggesting that more than one antigen may be involved in the pathogenesis of poststreptococcal GN.[17] These studies support the concept that streptococcal antigens localize in the glomerulus and initiate the inflammatory response by activating complement and inflammatory cells such as polymorphonuclear leukocytes and monocytes. Activated polymorphonuclear leukocytes release free radicals, reactive oxygen molecules, and protease enzymes, which can cause substantial tissue injury.[18] Studies have shown that apoptosis is evident in kidney biopsy specimens from patients with postinfectious GN in early and late stages and contributes to the resolution of glomerular hypercellularity.[19]

In contrast to other forms of hypocomplementemic GN, the long-term prognosis in postinfectious GN is excellent, and treatment is supportive therapy.[20] Most children require short-term diuretic and antihypertensive therapy. Gross hematuria resolves over several days, proteinuria decreases during the first several weeks after the acute episode, and microscopic hematuria may take several months to resolve. C3 should return to normal in 6 to 8 weeks, and if it remains depressed after this time, the diagnosis of postinfectious GN should be questioned, and another form of hypocomplementemic GN should be considered. Prolonged hypocomplementemia has been described, however, in a few children with postinfectious GN.[21] The inability to discontinue antihypertensive medications, lack of resolution of gross hematuria, and persistent high-grade proteinuria are each also signals that the underlying GN is not postinfectious, and that the child may need a kidney biopsy to determine a definitive diagnosis.

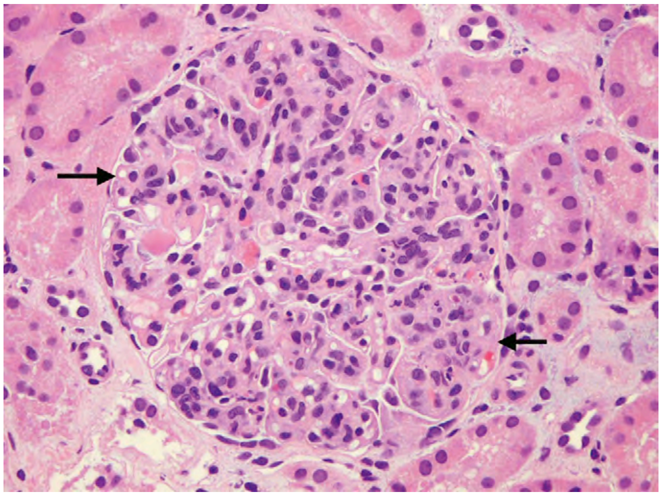

Figure 18-3 Light microscopy of a kidney biopsy specimen from a 13-year-old girl who presented with nephrotic syndrome and gross hematuria. Hematoxylin and eosin (H&E) stain shows proliferation with marked thickening of the glomerular basement membrane *(arrows)* and a peripheral lobular appearance of the glomerulus characteristic of membranoproliferative glomerulonephritis.

Membranoproliferative Glomerulonephritis

MPGN is also known as mesangiocapillary GN. MPGN is divided into three subtypes—type I, type II (dense deposit disease), and type III. Type I and type III are similar in their clinical, laboratory, and pathologic characteristics; kidney biopsy specimens from children with type II MPGN show distinct pathologic features, as described later.[22] In pediatric patients, 70% to 80% of the cases of MPGN are types I and III, and 20% to 30% are type II.[22] MPGN is very rare in toddlers and preschool-age children and is most common in adolescents. The age at onset of type I disease is slightly older compared with that of type II disease. In a large study of adult and pediatric patients with MPGN, the median age of presentation of type I disease was approximately 21 years versus 11.5 years for type II disease.[22] Other conditions associated with type II MPGN include partial lipodystrophy and ophthalmologic abnormalities in the retinal epithelium called *basal laminar drusen,* which were more advanced in patients with the longest duration of type II disease.[23]

Many children with MPGN present with nephrotic syndrome with or without gross hematuria, whereas a small percentage present with RPGN.[6,22,24] Many children eventually found to have MPGN are first found to have hematuria and proteinuria during a routine physical examination. Hypertension is present in approximately one fourth to one third of children early in the course of the disease.[7] Although clinical and laboratory findings cannot predict the subtype, it has been suggested that type III MPGN may be more likely to manifest with asymptomatic hematuria and proteinuria compared with types I and II.[8]

Urinalysis usually shows hematuria and proteinuria. Hematuria may be gross or microscopic. Proteinuria may range from a few hundred milligrams to several grams per day, leading to hypoalbuminemia, edema, and hyperlipidemia characteristic of the nephrotic syndrome. Unless the child has RPGN, blood urea nitrogen and creatinine levels at presentation are usually normal to slightly elevated. C3 is depressed in 70% to 90% of cases, and a low C3 is important in establishing a preliminary diagnosis of MPGN.[22] The depressed C3 does not correlate with prognosis, disease activity, or progression of the renal disease. As described earlier, the mechanism for the depressed serum C3 is complex and seems to be related to increased catabolism and decreased synthesis. The presence of C3 nephritic factor in 30% to 75% of cases contributes to increased catabolism of C3. C4 is usually normal in type II MPGN, but may be depressed in type I MPGN. This finding has been interpreted to suggest that the complement system is activated by the classic pathway in type I disease and by the alternative pathway in type II disease.

On light microscopy, thickening of the GBM, mesangial proliferation, and expansion of the mesangial matrix produce a characteristic lobular appearance of the glomeruli (Fig. 18-3). In type I MPGN, immunofluorescent studies show mesangial and GBM deposition of C3; IgG; and variable degrees of IgM, IgA, and other complement components. In type I MPGN, electron microscopy usually shows abundant subendothelial deposits and some deposits in the mesangium (Fig. 18-4). In type II MPGN, immunofluorescent studies usually show extensive GBM and mesangial deposition of C3, but a paucity of immunoglobulin deposition. Electron microscopy shows the characteristic dense deposits in the mesangium and within the GBM (Fig. 18-5). Electron microscopy in type III MPGN reveals subendothelial, intramembranous, and small subepithelial deposits (Fig. 18-6).

Because a low serum level of C3 is the laboratory hallmark of MPGN, abnormal regulation of the complement system particularly is thought to be central to the pathogenesis of MPGN.[6,25] Aberrant complement regulation is due to the presence of C3 nephritic factor, which is an autoantibody directed against the C3 convertase of the alternative pathway.[25] The binding of this antibody protects C3bBb from enzymatic inactivation so that there is continued C3 breakdown.[26] Genetic mutations of the factor H genotype have been implicated in the pathogenesis of type II MPGN.[27] Factor H is a soluble complement regulatory protein that has its primary role in regulating the activity of the alternative pathway, and factor H mutations are found in patients with type II MPGN.[28] Factor H gene mutations result in a lack of plasma factor H or in a functional defect in factor H proteins. Loss of factor H function also can be caused by inactivating factor H autoantibodies, C3 mutations preventing interaction between C3 and factor H, or autoantibodies against C3.[28]

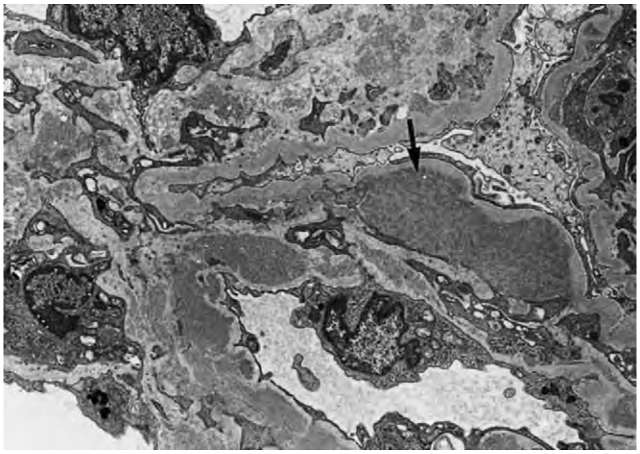

Figure 18-4 Electron micrograph shows a large subendothelial deposit *(arrow)* with mesangial interposition and mesangial deposits characteristic of membranoproliferative glomerulonephritis type I. (From Andreoli SP. Chronic glomerulonephritis in childhood: membranoproliferative glomerulonephritis, Henoch-Schönlein purpura nephritis, and IgA nephropathy. *Pediatr Clin North Am.* 1995;42: 1487-1504.)

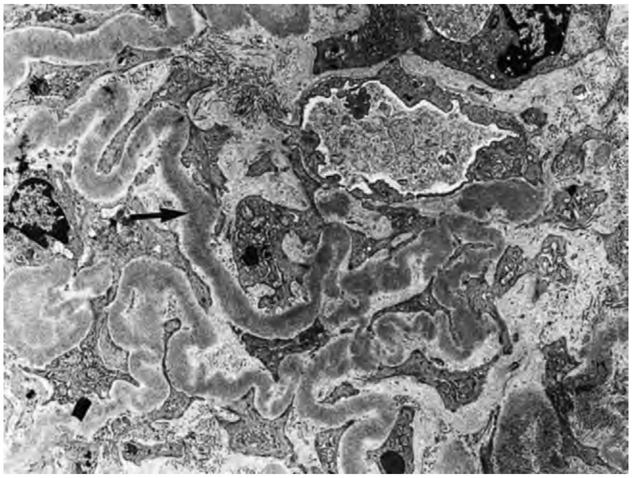

Figure 18-5 Electron micrograph shows intramembranous dense deposits *(arrow)* characteristic of membranoproliferative glomerulonephritis type II (dense deposit disease). The patient is a 10-year-old boy who presented with nephrotic syndrome, microscopic hematuria, and hypertension.

A strong association of MPGN and hepatitis C infection has been shown in adult patients, but such an association in pediatric patients is not apparent.[29-31] In adult patients, immunologic and virologic studies suggest that the renal disease is related to deposition within the glomeruli of immune complexes containing hepatitis C virus.[30]

Since MPGN was first described, it has been recognized to be a progressive GN, and the natural history is progression to end-stage renal disease. Without therapy, approximately 50% of children with MPGN have chronic kidney disease 10 to 11 years after diagnosis, and nearly 80% to 90% have chronic kidney disease 20 years after diagnosis.[4,6,7] Spontaneous resolution in the absence of specific therapy has been described, however.[32]

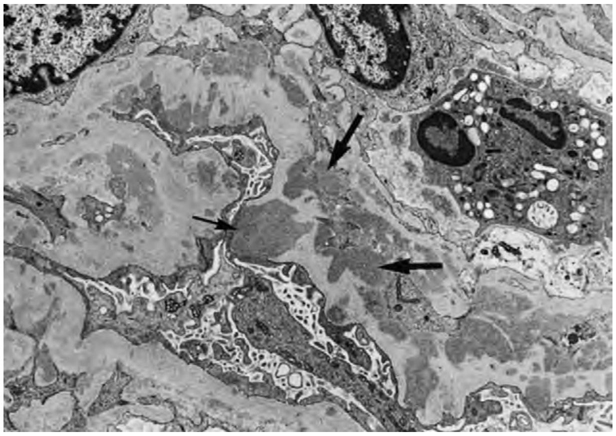

Figure 18-6 Electron micrograph shows subepithelial *(small arrow)* and subendothelial *(large arrows)* deposits characteristic of membranoproliferative glomerulonephritis type III. The patient is a 15-year-old boy who was found to have asymptomatic hematuria and proteinuria during a routine sports physical. (From Andreoli SP. Chronic glomerulonephritis in childhood: membranoproliferative glomerulonephritis, Henoch-Schönlein purpura nephritis, and IgA nephropathy. *Pediatr Clin North Am.* 1995;42:1487-1504.)

The poor prognosis of untreated MPGN has led to many different therapies, including anticoagulant therapy, antiplatelet therapy, and immunosuppressive therapy. Although there is not a universally accepted form of therapy for MPGN, therapy with alternate-day prednisone is used by most pediatric nephrologists. Prednisone therapy at a dose of approximately 2 mg/kg (with a maximum dose of 60 to 80 mg) is usually initiated after diagnosis and continued for a variable period followed by gradual reduction.[33] A double-blinded, placebo-controlled study using alternate-day prednisone showed that progression to chronic renal failure was delayed in children receiving alternate-day prednisone.[4] In uncontrolled studies, therapy with pulse methylprednisolone followed by alternate-day prednisone has been associated with improved outcome compared with the natural history of the disease.[24,34] It has been suggested that patients with type I MPGN have a better response to corticosteroid therapy than children with type III MPGN.[35]

Types I and III recur in the renal transplant in approximately 20% to 30% of renal transplant recipients.[36] Graft loss because of recurrent disease is approximately 30% to 40%. Type II MPGN recurs in the renal transplant in 100% of cases; however, graft loss because of recurrent disease varies with reports ranging from 10% to 50%.[36,37] In a large retrospective study, 5-year graft survival for patients with type II MPGN was significantly worse compared with patients transplanted for other causes (50% ± 7.5% versus 74.3% ± 0.6%).[37]

Systemic Lupus Erythematosus

SLE in children is a multisystem disease that typically manifests with a wide variety of symptoms related to the systemic nature of SLE.[38-41] SLE is rare in the first decade of life and is much more common during adolescence, with a female-to-male predominance of approximately 9:1. African-American and Asian ethnic groups have a higher incidence of SLE, and the disease is more severe in these ethnic groups.[42] The incidence of renal disease in children with SLE is 82% with a range of 28% to 100%, depending on the study population.[39] Although most children with SLE have renal involvement, it is rarely the primary manifestation of SLE. Renal disease may manifest as asymptomatic hematuria or proteinuria or both, with or without hypertension.

Table 18-2 Clinical Manifestations of Systemic Lupus Erythematosus at Presentation in Children

Clinical Symptom	Affected (%)	Range (%)
Rash	68	14-94
Fever	78	54-94
Arthralgia	75	44-100
Cardiac disease	40	19-56
Neurologic disease	30	3-48
Renal disease	82	28-100

Adapted from Cameron JS. Lupus nephritis in childhood and adolescence. *Pediatr Nephrol*. 1994;8:230-249.

Renal function is usually normal, but some children present with renal insufficiency with or without RPGN. Other common manifestations include fever, arthralgias, rash, weight loss, and cardiovascular involvement (Table 18-2).

The laboratory findings in SLE include a high-titer positive antinuclear antibody (ANA) with circulating anti-DNA antibodies that can be detected with a positive crithidia, which is a small parasite that contains abundant double-stranded DNA. The ANAs can be directed against double-stranded native DNA or other antigens, including Ro, La, Sm, and ribonucleoprotein.[38] C3 and C4 are low in most children with active GN. The renal disease can manifest with hematuria with or without red blood cell casts and proteinuria that may range from mildly elevated to nephrotic syndrome to RPGN. The degree of urinary abnormalities has been shown to correlate with the pathologic findings in children with lupus nephritis.[43] Children with hematuria alone were more likely to have mild histologic findings on biopsy specimens, whereas children with nephrotic syndrome were more likely to have diffuse proliferative disease on kidney biopsy specimens.[38-44] Other laboratory findings include anemia, thrombocytopenia, leukopenia, hypergammaglobulinemia, and prolonged prothrombin and partial thromboplastin times, which may be associated with antiphospholipid antibodies. Antiphospholipid antibodies have been associated with thrombotic events in adults, but this association in children is less apparent.[45]

Most children with SLE need a kidney biopsy to determine the precise pathologic diagnosis and the appropriate therapy. Several pathologic classifications, including the World Health Organization (WHO) classification, have been used in pediatric patients. The WHO classification of lupus nephritis has been updated to include several descriptive terms and subclassifications to describe the histologic lesion better.[46] Any classification of the histologic findings needs to take into consideration the variability of the histologic findings from glomeruli to glomeruli in a biopsy specimen and the variability in serial biopsy specimens from an individual patient. Although the WHO classification is most commonly used to classify renal disease in children with lupus nephritis, other information, such as the activity and chronicity index, can be used to estimate prognosis and clinical pathologic correlations.[40,43,44]

Most studies show that children and adolescents with more severe forms of lupus nephritis (WHO class IV) are more likely to have hypertension, renal insufficiency, and nephrotic syndrome.[38-40,43,44] Immunofluorescent and electron microscopy studies show mesangial, subendothelial, and subepithelial deposits, depending on the histologic classification, whereas more proliferative lesions are more likely to have deposits that extend to the GBM. In the WHO classification, classes I to IV seem to be a continuum of the severity of pathology in lupus nephritis, whereas class V or the membranous pattern of injury does not commonly evolve from other histologic patterns. In class V lesions, immunofluorescent and electron microscopy findings show subepithelial deposits characteristic of the membranous lesion.

The role of ANAs in the pathogenesis of SLE is uncertain. Inherited defects of the immune system, such as defects in production of serum complement components and certain histocompatibility groups, are risk factors for the development of SLE. Other studies have shown that genetic polymorphisms of the 1q23-24 segment of chromosome 1 and the C-reactive protein locus are linked with SLE in many populations.[42,48] The major hallmark of SLE is activation of the immune system, and children and adolescents with SLE show polyclonal B cell activation with failure to regulate B cell activation appropriately, with resultant production of multiple autoantibodies and the formation of immune complexes. Immune complexes composed of strongly complement activating antibodies are more pathogenic than immune complexes that activate complement less actively.[38]

The long-term morbidity and mortality of SLE are related to the renal disease, and because adolescents develop SLE at a young age, optimal management and therapy of SLE nephritis are very important. The severity of the pathologic changes on biopsy specimens is important in the choice of potential therapy. Although a uniform consensus in regard to therapy for mild mesangial and focal proliferative lupus nephritis does not exist, most studies suggest that corticosteroids are adequate therapy for the milder forms of lupus nephritis.[39] In diffuse proliferative lupus nephritis, several studies have shown that the addition of cytotoxic agents (oral cyclophosphamide, azathioprine, or intermittent intravenous cyclophosphamide) significantly improves the long-term outcome compared with prednisone alone.[38,48,49] Patients receiving prednisone and a cytotoxic agent showed improved control of the clinical signs of renal disease and fewer chronic changes on follow-up biopsy specimens.[48-50]

A regimen of monthly intravenous cyclophosphamide for approximately 6 months and then every 3 months has shown improved renal survival compared with other regimens.[49] The prolonged use of high-dose cyclophosphamide has been associated with higher morbidity, however, owing to infections and other complications.[42,51-54] More recent studies in adults have shown that lower dose cyclophosphamide or mycophenolate mofetil have similar long-term outcomes as high-dose cyclophosphamide with less morbidity.[51-54] Rituximab therapy for lupus nephritis is in clinical trials and may become a common therapy for lupus.[55]

Administration of cyclophosphamide to adolescent patients has important implications for long-term gonadal function. The incidence of amenorrhea depends on the age at the time of administration and the total number of doses that the patient has received.[56] Children may need antihypertensive and diuretic therapy as well. Recurrence of lupus nephritis in the transplanted kidney is uncommon, and graft survival is similar in patients transplanted with other diseases.[57] The immunologic abnormalities resulting in active SLE are thought to abate after the development of end-stage renal disease such that recurrent disease in the allograft is unusual.

Nephritis of Chronic Infection

Historically, the common infections causing nephritis of chronic infection were bacterial endocarditis and nephritis associated with an infected atrioventricular shunt. In the current era of antibiotic prophylaxis for subacute bacterial endocarditis and the use of ventriculoperitoneal shunts rather than ventriculoatrial shunts, these infections are uncommon. Currently, chronic infections with hepatitis viruses, human immunodeficiency virus (HIV), and syphilis are more important in the United States, whereas malaria, parasitic infection, and HIV are more common in developing countries. Although not invariably the case, the symptoms of the primary infection are usually the predominant clinical manifestation, and glomerular disease is a secondary issue that may be noted only incidentally. In nephritis of chronic infection, hematuria and proteinuria of some degree are usually present. The serum C3 level is usually depressed by uncertain mechanisms, but it is presumed to be due to activation of the immune system as a result of chronic deposition of antigen with in situ immune complex formation or deposition of circulating immune complexes. Rheumatoid factor also may be positive, presumably as a result of the formation of antibodies resulting from chronic immune stimulation.

The pathology of nephritis of chronic infection varies and may range from mild mesangial proliferation with or without focal crescent formation to RPGN in severe cases. Immunofluorescent studies are usually positive, reflecting the presumed underlying immune complex pathophysiologic mechanisms of the disease. Immune complex deposits evident on electron microscopy are quite variable because deposits may be located in the mesangial areas or in subendothelial or subepithelial locations. Therapy for nephritis of chronic infection is directed at treating the underlying infection because eradication of the infection should eliminate further renal injury.

IMMUNOGLOBULIN A–RELATED GLOMERULONEPHRITIS

Several different renal diseases are associated with predominant deposits of IgA in the kidney, including IgA nephropathy, HSP, and SLE (see Table 18-1). IgA nephropathy has been described as the most common GN leading to chronic kidney disease worldwide.[9,59] HSP is a common vasculitic lesion in children with a peak incidence at 4 to 5 years of age. Most patients with HSP do not develop chronic kidney disease, but complications from HSP nephritis may not become apparent until adulthood. A long-term follow-up study showed that many pregnancies in women who had HSP nephritis during childhood were complicated by proteinuria or hypertension or both.[60] Complications of pregnancy occurred even in women who had no active signs of renal disease before pregnancy.

The relationship of HSP nephritis and IgA nephropathy is uncertain. It has been suggested that IgA nephropathy is HSP nephritis without the rash.[61,62] A report describes the development of IgA nephropathy in one identical twin while the other developed HSP after adenoviral infection in each.[61] The renal pathologic features in HSP nephritis and IgA nephropathy are very similar, and clinical characteristics of severe renal disease are similar in IgA nephropathy and in HSP nephritis. The clinical manifestations, laboratory and pathologic findings, pathophysiology, and potential treatment strategies for IgA nephropathy and HSP nephritis are discussed in this section; GN associated with SLE, which also may be associated with predominant IgA deposits, is reviewed in the section Hypocomplementemic Glomerulonephritides.

Immunoglobulin A Nephropathy

IgA nephropathy was first described in the late 1960s by the French pathologist Berger[63]; IgA nephropathy has also been called Berger disease. IgA nephropathy affects males more commonly than females and is rare in blacks.[64] In pediatric patients, the most common clinical presentation of IgA nephropathy is recurrent episodes of painless, gross hematuria occurring within 1 to 3 days after an upper respiratory tract infection. The gross hematuria generally resolves over the next several days, but recurs after additional viral or bacterial infections. This presentation of IgA nephropathy differs from postinfectious GN in the short latency period between the infection and the onset of hematuria, in the absence of features of an acute nephritic syndrome, and in the recurrent nature of the gross hematuria with illness over the course of several years. Microscopic hematuria with or without proteinuria may persist between episodes of gross hematuria. IgA nephropathy also may manifest with asymptomatic microscopic hematuria with or without proteinuria. A few children with IgA nephropathy present with hypertension, nephrotic syndrome, or RPGN.

IgA nephropathy was originally thought to be a benign GN, but long-term follow-up has shown that many patients eventually develop chronic kidney disease.[65-69] It is estimated that 20% to 40% of children and adults with IgA nephropathy develop progressive glomerulosclerosis, interstitial fibrosis, and chronic kidney disease.[9,59,65-69] Various clinical, laboratory, and histologic findings are associated with a higher risk for progressive disease, and it is this subset of children who should be targeted for potential therapy. Urinary loss of podocytes is associated with progressive disease in children with IgA nephropathy and HSP nephritis.[70]

Hematuria is nearly always found on urinalysis, whereas the degree of proteinuria varies, ranging from normal to several grams per day. Multiple studies in adult and pediatric patients have shown that persistent proteinuria is the best laboratory indicator of renal disease that is likely to progress to chronic renal failure. The magnitude of proteinuria correlates with the presence and degree of segmental sclerosis, crescent formation, and interstitial changes on biopsy specimens and with deposition of IgA adjacent to the GBM and in the mesangium.[65,66] The serum C3 level is normal in IgA nephropathy, differentiating it from postinfectious GN and MPGN. Although the serum C3 level is normal, signs of complement activation are found in many patients with sensitive assays that detect fragments of activated C3.[71] Renal function is usually normal at presentation, but a few children have a mildly depressed glomerular filtration rate.

Screening blood tests for IgA nephropathy, including tests for circulating IgA-containing immune complexes and IgA-fibronectin aggregates in patients with IgA nephropathy, and increased levels of IgA have been suggested to correlate with IgA nephropathy. Each of these abnormalities is noted in a variable number of patients with IgA nephropathy, however, and these tests lack sufficient sensitivity to be of any diagnostic or prognostic value. The only mechanism to diagnose IgA nephropathy with certainty is a kidney biopsy.

The histologic features of IgA nephropathy range from minimal and minor changes to focal or diffuse mesangial proliferation; segmental sclerosis and crescent formation may be seen in severe cases (Fig. 18-7).[5,66,67] The presence of segmental sclerosis on a biopsy specimen is associated with proteinuria; interstitial fibrosis and tubular atrophy also are seen in severe cases and are associated with development of chronic kidney disease. IgA nephropathy was so named because immunofluorescent studies show predominant IgA deposition in the mesangium with lesser amounts of IgG and IgM (Fig. 18-8). In severe cases, IgA extends to the GBM. GBM deposition of IgA also is associated with proteinuria and the development of chronic renal disease in some studies.[65] C3 is usually deposited in a distribution similar to that of IgA.

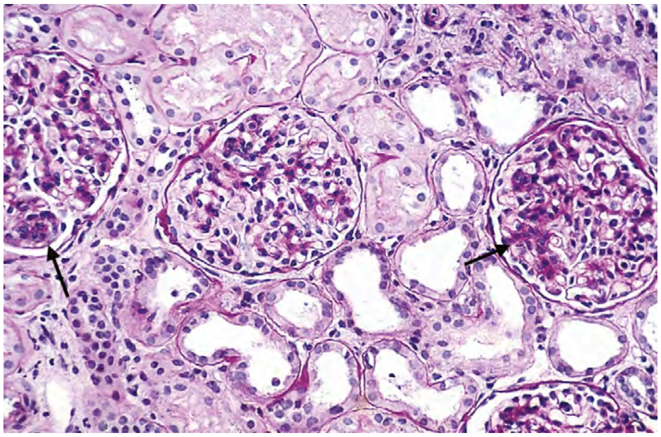

Figure 18-7 Light microscopy of a kidney biopsy specimen from a 12-year-old boy who had recurrent hematuria 1 to 2 days after an upper respiratory tract infection. He had microscopic hematuria between episodes of gross hematuria and normal protein excretion and normal blood pressure. Hematoxylin and eosin (H&E) stain shows focal and segmental focal proliferation *(arrows)*. The clinical characteristics of normal protein excretion with normal blood pressure and the absence of segmental glomerulosclerosis or interstitial fibrosis on biopsy specimen suggest a good prognosis, but the need for long-term follow-up.

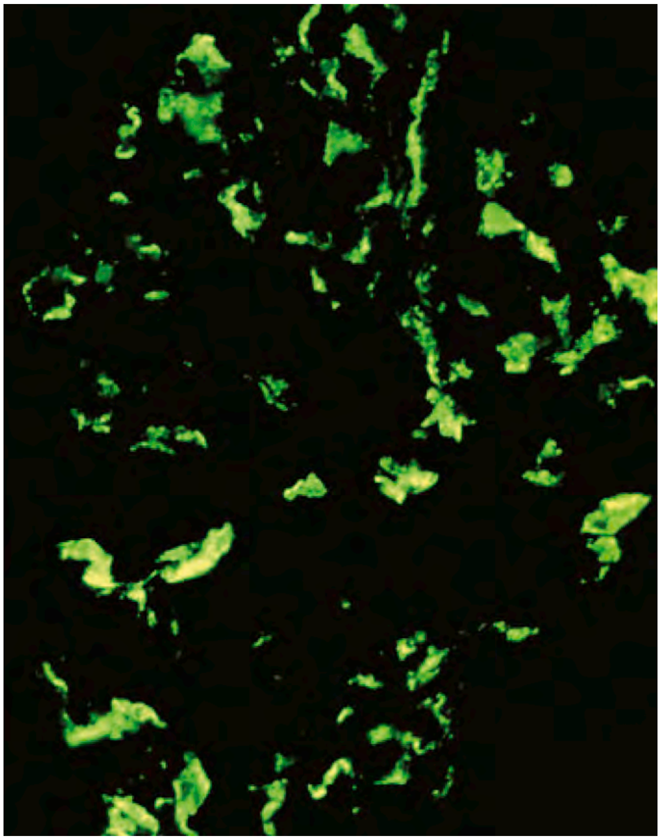

Figure 18-8 Typical immunofluorescent appearance of mesangial IgA deposition in a glomerulus in a kidney biopsy specimen from the 12-year-old boy described in Figure 18-7.

The deposition of properdin, an alternate complement pathway protein, suggests that complement is activated by the alternate pathway.[72] Electron microscopic studies show deposits in the mesangium and paramesangial areas in typical cases, whereas deposits on the GBM are noted in severe cases.

The pathogenesis of IgA nephropathy remains obscure despite extensive investigation of the physiology of IgA production in humans and the immunobiology of IgA in IgA nephropathy.[73,74] As in HSP nephritis, altered production of mucosal IgA after infection may play a role in the pathogenesis of the disease, but production of IgA derived from the bone marrow is also increased in patients with IgA nephropathy. Familial studies have shown a slightly increased familial incidence of the disease, suggesting that genetic factors also play a role in pathogenesis.[74] Several studies have shown that genetic polymorphism of the angiotensin-converting enzyme gene may play a role in the progression of IgA nephropathy to chronic renal failure.[75] Other genetic polymorphisms that might influence the susceptibility and clinical course of IgA nephropathy include polymorphisms of the interleukin-1 receptor antagonist allele and allelic mutations of the platelet-activating factor acetylhydrolase gene.[75-77]

A proven form of therapy for IgA nephropathy does not exist. Children without clinical, laboratory, or histologic features of progressive disease should be managed by long-term observation with careful follow-up to determine whether the child is developing hypertension, increasing proteinuria, or declining renal function suggestive of progressive disease. These children do not require therapy, but need periodic pressure determination, urinalysis, quantitation of proteinuria, and determination of renal function.

Hypertension, renal insufficiency, and persistent proteinuria are clinical predictors of progressive disease, as are the pathologic features of segmental sclerosis, crescent formation, interstitial fibrosis, and tubular atrophy.[10,65-67,78] Children who show these clinical, laboratory, or pathologic characteristics are candidates for therapy. Some studies suggest that immunosuppressive therapy results in stabilization of the disease and retards or prevents progression of the renal disease,[10,78] whereas others do not support a role for immunosuppressive therapy in IgA nephropathy.[79] In a study using alternate-day prednisone therapy in children with risk factors for progressive disease, treated children had decreased proteinuria and decreased hematuria compared with historic controls.[78] In an uncontrolled study, children with severe IgA nephropathy were treated with prednisone and azathioprine, with a reduction in hematuria and proteinuria.[10]

In adults with IgA nephropathy, daily administration of omega-3 fatty acids in fish oil was found to result in decreased proteinuria and stabilization of renal function compared with patients who received placebo.[80] Other studies using fish oil concluded that it was of no benefit, however, and a more recent meta-analysis was inconclusive.[81,82] A randomized placebo-controlled trial in children and young adults did not show any benefit of therapy with fish oil in IgA nephropathy.[83]

In a randomized controlled trial in adult patients with IgA nephropathy,[84] therapy with corticosteroids for 6 months protected against deterioration of renal function without notable adverse side effects. Other studies have shown that children with IgA nephropathy who were treated with prednisolone, azathioprine, and anticoagulants soon after diagnosis had fewer sclerosed glomeruli in follow-up biopsy specimens, suggesting that therapy preserved renal function.[85] Steroid therapy in adults with severe IgA nephropathy was found to decrease proteinuria and protect against renal function deterioration.[86] One study of therapy with mycophenolate mofetil in patients with IgA nephropathy showed benefit, whereas a second showed that therapy with mycophenolate mofetil was not beneficial.[87,88] Additional studies are needed to determine the optimal therapy for children with IgA nephropathy.[89,90]

In patients who progress to end-stage renal disease, IgA deposits in the transplanted kidney have been shown to recur in 50% of patients, and a higher recurrence rate may be seen in recipients of living-related transplants. This recurrence is thought to be due to the genetic susceptibility of the disease. Although recurrence is common, allograft loss because of IgA deposition and recurrent disease is rare.[36]

Henoch-Schönlein Purpura

The typical clinical features of HSP include rash, gastrointestinal disease, arthritis, and renal disease. Several other organs, including the central nervous system, cardiopulmonary system, and musculoskeletal system, also may be affected by leukocytoclastic vasculitis characteristic of HSP. Most children do not have severe renal disease and do not experience serious sequelae after HSP, but a few children do develop serious renal disease, which accounts for the major morbidity of HSP.[91,92] HSP typically occurs in younger children with a peak age incidence of 4 to 5 years. Although HSP is less common in older children and adolescents, older children with HSP seem to be at higher risk for severe renal disease. Renal disease in unselected patients with HSP has been estimated to range from 20% to 50%.[92] Typically, children who develop renal disease have hematuria with or without proteinuria within the first 2 to 3 months from the onset of the rash.

More recent studies have shown that genetic polymorphisms may predispose to the development of HSP or have a role in the evolution to HSP nephritis, or both. In a study of 57 patients with HSP, no significant differences were found in the allele or genotype frequencies for two vascular endothelial cell growth factor (VGEF) polymorphisms between patients with HSP and control patients, but the high VGEF producer allele was increased in patients with HSP nephritis compared with healthy controls.[93] Polymorphisms of the interleukin-1β gene were not different in patients with HSP compared with controls, but each of the 5 patients who developed severe nephropathy carried the rare T allele compared with 16 of the remaining 44 patients.[94]

Other studies showed that the TT genotype of the C-509T polymorphism of the transforming growth factor-β gene was significantly more common in children with HSP compared with control children, and the TT genotype was more common in children with severe HSP.[95] Polymorphism of the renin-angiotensin system also has been associated with the development of HSP and possibly the development of renal disease.[96] Patients with familial Mediterranean fever have a higher incidence of HSP, with approximately 5% of patients with familial Mediterranean fever developing HSP.[97] Other studies have shown no association with uteroglobin gene polymorphism in childhood HSP.[98] Similarly, polymorphisms in thrombophilia genes, including methylenetetrahydrofolate reductase, prothrombin, and factor V genes, did not differ in patients with HSP and controls.[99] Although more studies are needed, these early studies suggest that there may be a genetically determined susceptibility to risk and severity of HSP nephritis.

Hematuria is the first indication of renal involvement in HSP nephritis, and most children with renal involvement have isolated hematuria. Some children have low-grade proteinuria in addition to hematuria, however. Urinary abnormalities in children with hematuria with or without low-grade proteinuria generally resolve spontaneously, and such children are at low risk for progressive renal disease and late complications. A smaller percentage of children with HSP nephritis have hematuria with high-grade proteinuria sufficient to result in hypoalbuminemia, edema, and the nephrotic syndrome, whereas a rare child presents with RPGN.[91,100]

When the clinical findings including the rash are characteristic of HSP, laboratory studies need to be performed to determine the extent of renal involvement. If the diagnosis is uncertain, vasculitis secondary to polyarteritis nodosa (PAN) or to SLE should be considered because each may manifest with rash and renal disease. ANA titers, complement studies, and antineutrophil cytoplasmic antibody (ANCA) studies, which may be positive in PAN, evaluate for other forms of vasculitis.[101] Children with HSP nephritis have hematuria, whereas children with more severe renal disease also have proteinuria. High-grade proteinuria may lead to the nephrotic syndrome, and hypoalbuminemia is usually due to urinary protein losses, but severe gastrointestinal involvement may occasionally result in a protein-losing gastroenteropathy with hypoalbuminemia owing to gastrointestinal protein losses. Serum complement concentrations are usually normal to slightly elevated.

Only a few children with HSP nephritis need a kidney biopsy. Early studies showed that microscopic hematuria with low-grade proteinuria is associated with only mild histologic alterations, and biopsy is not indicated in such cases. Children with a nephrotic or nephritic syndrome are more likely to show more severe histologic alterations on biopsy specimens and have a worse long-term prognosis. Increasing proteinuria, nephrotic syndrome, and renal insufficiency are indications for a kidney biopsy.

Pathologic findings range from mild mesangial proliferation in mild cases to severe crescentic disease in cases of RPGN. When renal involvement is mild, light microscopy may be normal or show only mild mesangial proliferation in a focal and segmental distribution. Mesangial proliferation is diffuse and more pronounced in some cases, and polymorphonuclear leukocyte infiltration may be prominent and may be associated with necrosis. The histologic findings and the percentage of glomeruli that show crescent formation in particular are thought to be predictive of long-term outcome, and potential therapy should be directed to patients at higher risk for chronic renal disease. Immunofluorescent studies show mesangial IgA deposition usually greater than IgG and IgM deposition in the mesangium, with extension to the GBM in some cases. Fibrinogen and complement deposition also are common, and electron microscopy studies show dense deposits in the mesangium and paramesangial areas.

The pathogenetic mechanisms that initiate HSP are unknown. Because an upper respiratory infection frequently occurs before the onset of HSP, and because IgA is typically found in the kidney and in extrarenal sites, it has been suggested that abnormal mucosal IgA production after an infection may precipitate the vasculitis. Early reports suggested that streptococcal infections frequently preceded the development of HSP, but evidence for a role for streptococcal infection in the pathogenesis of HSP has not been documented.[102] Elevated levels of IgA-containing immune complexes, IgA rheumatoid factor, and IgA-fibronectin complexes, and the presence of mesangial cell autoantigens in some patients support the role of immune dysregulation in the pathogenesis of the vasculitis.[103]

Children with active HSP should be monitored for the development of renal involvement until the disease subsides. Increasing proteinuria is a signal for severe disease, and the development of the nephrotic syndrome or renal insufficiency generally indicates the need for a biopsy. Previous studies have shown that most children who presented with hematuria and low-grade proteinuria had an excellent long-term prognosis, with normal renal function, normal urinalysis, and normal blood pressure at follow-up, but a few had renal abnormalities. In contrast, several children who presented with an acute nephritic syndrome, nephrotic syndrome, or both had hypertension and impaired renal function during long-term follow-up.[60] In this study, many pregnancies in women who had HSP nephritis during childhood were complicated by proteinuria or hypertension or both, and complications of pregnancy occurred even in women who had no active signs of renal disease before pregnancy.

Corticosteroid therapy is effective for the treatment of the acute gastrointestinal manifestations of HSP, but a role for corticosteroids in the management of HSP nephritis remains controversial. In a retrospective study comparing children treated with steroids for gastrointestinal disease with children who did not receive steroids, the subsequent incidence of nephropathy was similar, suggesting that corticosteroids do not prevent HSP nephritis.[104] In contrast, a prospective study suggested that children receiving prednisone had a reduced incidence of renal involvement.[105] Only children who have clinical findings and histologic features suggestive of severe disease should be potential candidates for therapy. Therapy with corticosteroids with or without other immunosuppressive agents has been used in several studies, but a proven, effective, accepted therapy for severe HSP nephritis is unavailable. Given the natural history of severe HSP nephritis, a trial of therapy is reasonable to attempt to decrease the incidence and severity of long-term renal disease.

HSP nephritis may occur after renal transplantation, although the incidence seems to be low, estimated at less than 10% to 35%.[106] Histologic recurrence of IgA deposits in the allograft is more common than clinical recurrence and seems to be more common when patients are transplanted within 18 to 36 months of active disease. Graft loss because of recurrent disease is more likely if histologic recurrence is accompanied by clinical recurrence, including hematuria, proteinuria, and purpuric lesions.

MEMBRANOUS GLOMERULONEPHRITIS

Membranous GN is frequently called membranous glomerulopathy or membranous nephropathy because there is little to no inflammation detectable on light microscopy. Membranous GN is much more common in adult patients than in pediatric patients. In the International Study of Kidney Diseases in Children, less than 1% of children with nephrotic syndrome were found to have membranous GN.[107,108] Most children present with nephrotic syndrome and have microscopic hematuria.[109,110] Asymptomatic proteinuria and gross hematuria are less common presentations. Most children are normotensive, but 20% to 30% have some degree of hypertension.

Membranous GN may be idiopathic or secondary. Secondary forms of membranous GN are associated with collagen vascular diseases such as SLE and autoimmune diseases such as Crohn disease. Secondary forms of membranous GN also are associated with drug exposure or more commonly with chronic infections, such as hepatitis B, syphilis, malaria, and other parasitic infections. Similar infections are associated with nephritis of chronic infection, and hypocomplementemia may be seen in secondary cases of membranous GN, suggesting an overlap between nephritis of chronic infection and membranous GN associated with chronic infection.

At presentation, renal function is usually normal, but some children develop a progressive course and eventually develop chronic renal failure.[110] Complement levels are normal, and serologic studies are negative, unless the child has the membranous form of lupus nephritis, in which case the ANA and anticirculating DNA antibodies are positive. As mentioned previously, serologic studies for hepatitis B or other chronic infections may be positive. The incidence of a depressed C3 level is low in idiopathic cases, whereas one study reported a very high incidence of 64% in a highly selected group of children with membranous GN and chronic hepatitis B antigenemia.[111]

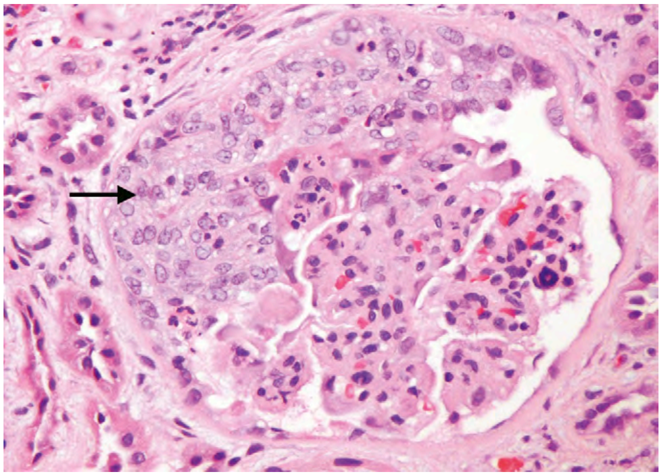

Figure 18-9 Cellular crescent in a kidney biopsy specimen from a 15-year-old girl who presented with gross hematuria, edema, hypertension, and rapidly deteriorating renal function. Hematoxylin and eosin (H&E) stain shows proliferative glomerulonephritis with a cellular crescent *(arrow)* involving about 50% of the glomeruli.

Light microscopy shows substantial thickening of the GBM with little to no inflammation of resident glomerular cells, and there is little to no inflammatory infiltrate. Immunofluorescent studies show marked deposition of IgG and complement on the GBM, with electron microscopy studies showing subepithelial spikes corresponding to the location of the IgG and C3 deposits noted on immunofluorescent microscopy.

The natural history of membranous GN in pediatric and adult patients varies, with one third of adults and a substantial percentage of pediatric patients entering remission in the absence of therapy.[109] Only children with risk factors for progressive disease are candidates for therapy; risk factors include persistent nephrotic syndrome, renal insufficiency, and hypertension.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Postinfectious GN, MPGN, HSP, and nephritis associated with SLE each cause RPGN in a small percentage of patients. In contrast, ANCA-positive GN, anti-GBM disease, and Goodpasture syndrome typically manifest with clinical and pathologic characteristics of RPGN. The clinical and laboratory characteristics of RPGN include hematuria, which may be gross or microscopic, proteinuria, edema, hypertension, and rapidly deteriorating renal function. Urinalysis shows a very active sediment with red blood cell casts. When RPGN is suspected, prompt biopsy to determine a definitive diagnosis and the initiation of therapy is essential to preserve renal function.

The characteristic pathologic feature of RPGN is extensive crescent formation, usually involving more than 50% of the glomeruli (Figs. 18-9 and 18-10). Crescent formation results from proliferation of epithelial cells in the Bowman capsule and activation of monocytes and fibroblasts. Depending on

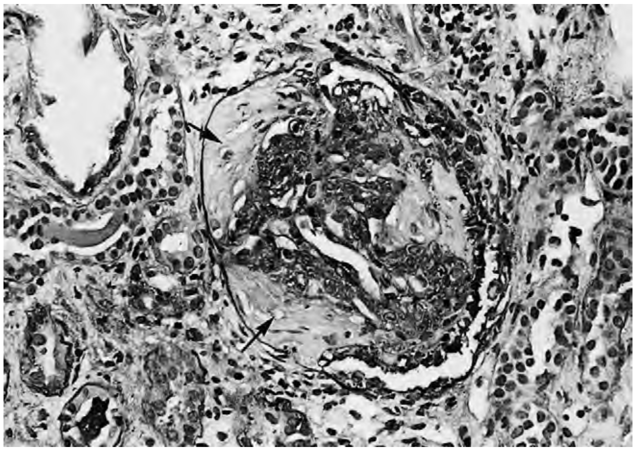

Figure 18-10 Fibrocellular crescent in a kidney biopsy specimen from a 16-year-old boy who presented with a creatinine value of 22.2 mg/dL, blood urea nitrogen of 226 mg/dL, a history of intermittent gross hematuria for 1 month, and symptoms of lethargy. The antineutrophil cytoplasmic antibody (ANCA) was strongly positive in a P-ANCA pattern. Hematoxylin and eosin (H&E) stain shows fibrous crescents *(arrows)* in a segmental distribution in a glomerulus. Other glomeruli showed cellular, fibrocellular, and fibrous crescents.

the duration of the RPGN, fresh crescents appear cellular, whereas older crescents may have evolved to a fibrocellular form (see Figure 18-10). The prognosis of RPGN depends on the underlying etiology and the prompt initiation of therapy when indicated.

Antineutrophil Cytoplasmic Antibody–Associated Glomerulonephritis

ANCA-positive vasculitis and GN occur in Wegener granulomatosis, PAN, and pauci-immune RPGN. ANCAs react against cytoplasmic constituents of polymorphonuclear leukocytes and monocytes. Most cytoplasmic-staining ANCAs (C-ANCAs) react with proteinase-3 in neutrophils and monocytes, whereas most perinuclear-staining ANCAs (P-ANCAs) react with myeloperoxidase. Although there is considerable overlap, C-ANCAs are more commonly found in patients with Wegener granulomatosis, and P-ANCAs are more common in patients with pauci-immune RPGN; the incidence and type of ANCAs in PAN vary.[112-114] The role of ANCAs in the pathogenesis of vasculitis is unknown, but studies have shown that ANCAs stimulate production of free radicals such as superoxide dismutase by human neutrophils, and that ANCA-activated neutrophils can induce tissue injury.[115] Monocytes and cytokines are also thought to play a role in the pathogenesis of the vasculitis.[116]

P-ANCA-positive pauci-immune RPGN is the most common ANCA-positive associated disease in pediatric patients. Children present with clinical characteristics of RPGN and are found to have extensive crescent formation on biopsy specimen with a relative paucity of immune deposits on immunofluorescent and electron microscopy studies—hence the name pauci-immune RPGN. Many children with ANCA-positive RPGN progress to end-stage renal disease, and children who present with advanced disease and severe renal insufficiency are less likely to recover renal function.[116] Early diagnosis and prompt therapy with intravenous methylprednisolone (Solu-Medrol) followed by oral corticosteroids and either intravenous or oral cyclophosphamide have been shown to improve long-term outcome in adult and pediatric patients.[112-116]

Wegener granulomatosis is rare in pediatric patients, but symptoms in pediatric patients have been described as similar to symptoms that occur in adult patients, including sinusitis and pulmonary infiltrates, rash, and renal disease.[117,118] Similarly, children with microscopic PAN usually have systemic symptoms, but renal involvement in microscopic PAN is an important cause of morbidity and mortality.[119] Prompt diagnosis and therapy with intravenous steroids and intravenous or oral cyclophosphamide offer the best chance to preserve renal function.

Anti–Glomerular Basement Membrane Antibody Disease and Goodpasture Syndrome

Anti-GBM antibody disease is also called Goodpasture syndrome when accompanied by pulmonary hemorrhage. The combination of GN and pulmonary symptoms, including pulmonary hemorrhage, in pediatric patients is more likely due to SLE, HSP, PAN, or other ANCA-positive diseases rather than Goodpasture syndrome. Anti-GBM antibody disease is rare in children; at the author's institution, which serves a population of more than 5 million annually, only two cases of Goodpasture syndrome in a pediatric patient have been seen since about 1980.

Although quite rare, the clinical presentation of pulmonary hemorrhage with RPGN and the characteristic pathology of linear deposition of IgG on the GBM on immunofluorescent studies are quite distinct.[120] The pathology typically shows severe necrotizing GN with crescents in more than 50% of the glomeruli.[120] Anti-GBM antibodies are directed against the a3 chain of type IV collagen in the GBM, and they cross-react with collagen molecules in the pulmonary microvasculature, leading to GN and pulmonary hemorrhage.[121] Environmental factors, including infections and exposure to toxic agents, have been implicated in precipitating the syndrome.[122] Although anti-GBM antibody disease and Goodpasture syndrome are rare, prompt diagnosis is important so that frequent plasma exchange can be instituted to remove existing anti-GBM antibody. Therapy with intravenous corticosteroids and cyclophosphamide can be initiated to prevent further production of the autoantibody. Most children develop chronic kidney disease, and in anti-GBM antibody-mediated GN, renal transplantation is not undertaken until the anti-GBM titer is negative, and clinical symptoms are absent.

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PART III

UPPER URINARY TRACT

SECTION 1

CONGENITAL URINE FLOW IMPAIRMENTS

CHAPTER 19

CONGENITAL URINE FLOW IMPAIRMENTS OF THE UPPER URINARY TRACT: PATHOPHYSIOLOGY AND EXPERIMENTAL STUDIES

Craig A. Peters

Obstruction of the upper urinary tract presents a significant clinical challenge to pediatric urologists, not as much in surgically managing these conditions, but in determining which patients may be benefited by therapy, and whether there may be more effective means of improving the function of obstructed kidneys. The ultimate key to unraveling these questions lies in an understanding of the mechanisms and pathophysiology of congenital urinary obstruction. This chapter reviews the basic pathophysiologic themes of upper urinary tract obstruction with an emphasis on the effects of obstruction on the developing kidney. These pathophysiologic mechanisms are similar to those affecting the kidney in lower urinary tract obstruction.

DEFINITIONS AND PATHOPHYSIOLOGY

Ureteropelvic Junction and Ureterovesical Junction Obstruction

Ureteropelvic junction (UPJ) obstruction is defined as impaired urine flow from the pelvis into the proximal ureter, causing dilation of the collecting system and potential renal damage. Classified as intrinsic, extrinsic, or secondary, this common renal anomaly of childhood is seen in all pediatric age groups and is the most common cause of neonatal hydronephrosis.[1] *Ureterovesical junction (UVJ) obstruction* is an obstructive condition of the distal ureter as it enters the bladder. Although commonly called an obstructed megaureter, UVJ obstruction is a more specific term, and focuses on the obstructive nature of the lesion. UVJ obstruction may be primary or secondary; the latter is due to extrinsic compression of the ureter by a thick bladder wall in various pathologic states.

The overall incidence of UPJ obstruction approximates 1 in 1500.[2] The ratio of males to females is 2:1 in the neonatal period, with left-sided lesions occurring in 60%.[3-5] The lower pole moiety is usually affected in renal duplication anomalies. In the newborn period, a unilateral process is more common,[6,7] but bilaterality has been found in 10% to 40% of neonates in some series.[1,3]

Definition of Obstruction

More problematic is the definition of obstruction, which continues to elude the pediatric urologic community. Koff's[8] definition was a valuable contribution to the conceptualization of obstruction when he wrote that obstruction is "any restriction to urinary outflow, that left untreated will cause progressive renal deterioration." This definition needs to be expanded in the context of congenital obstruction, which may affect normal development of the kidney, limiting normal increases in function, but not producing a decline in function.[9] A child's kidney needs to increase its function significantly in the first years of life, and obstruction may constrain its normal maturation. If a kidney at birth is functioning at a lesser degree than normal associated with a potentially obstructive lesion, the "loss of function" may have already occurred before a time when it could be measured. This makes the condition no less obstructive, and raises the concern for potential further loss of absolute or potential function. The abnormally low function may be viewed as an indication of impaired maturation (i.e., no function has been "lost," but the normal level of function has not been achieved). How one acts in these situations is not determined by defining it as obstruction, but by the clinical context.

Obstruction is a spectrum of severity and effect. To attempt to divide between "obstructed" and "nonobstructed" as if they were black and white is erroneous to begin with. This dichotomous view of obstruction has, to some extent, clouded clinical thinking about obstructive conditions in children. It may be reasonable to say that because complete obstruction is rarely present, none of these systems are truly obstructed. It also may be reasonable, however, to admit that all primary hydronephrosis (i.e., not due to reflux or having been previously intervened on) is due to *some* degree of obstruction. It may be insufficient to warrant intervention, but underlying pathophysiologic mechanisms may be acting to *some* degree. It is the task of clinicians to sort out whether this obstruction poses any threat to the child's kidney, and what needs to be done about it. To make those determinations, a better understanding of the pathophysiology of upper urinary tract obstruction is essential.

Ureteral Pathology of Obstruction

Intrinsic and Extrinsic Disease

The anatomic basis of the obstruction is usually considered to be either intrinsic or extrinsic. Intrinsic obstruction is defined as an obstructive abnormality of the ureter with luminal narrowing with or without kinking and usually characterized by abnormalities of the ureteral wall. These are typically relative excesses of connective tissue and reduced amounts of smooth muscle.[10] There is wide variation in the external and pathologic appearance of intrinsic UPJ obstruction, although there is almost always a patent lumen detectable. The functional character of an intrinsic obstruction cannot be differentiated from extrinsic obstruction and may produce a constant resistance to urine flow, but may also produce intermittent obstruction. This pattern of obstruction is flow dependent, where a threshold flow rate would induce obstruction owing to a configuration change of the UPJ.[11]

Although intrinsic pathology is the most common etiology of neonatal UPJ obstruction, episodic obstruction secondary to intermittent kinking at the UPJ occurs more often in older children and young adults. If the renal pelvis cannot compensate for an acute increase in urinary output, transient obstruction results in acute flank pain and nausea (when bilateral, this has been called Dietl crisis).[12]

Extrinsic UPJ obstruction is usually caused by proximal ureteral compression by "anomalous" renal vasculature to the lower pole of the kidney. It is theorized that the proximal ureter may drape and flatten over anteriorly passing accessory or aberrant vessels, or a two-point obstruction is created between the fixed UPJ and the crossing vessel.[13,14] These obstructions may be intermittent as well.

Secondary UPJ obstruction may develop as a consequence of severe vesicoureteral reflux in which a tortuous ureter may kink proximally.[15] Previous reports have described vesicoureteral reflux in 15% of children with UPJ,[16,17] although the fraction that is secondary to the reflux is difficult to determine, and the actual diagnosis may be difficult.[18]

Most cases of UPJ obstruction are diagnosed in the perinatal period because of the now common use of prenatal ultrasonography.[19] Hydronephrosis of the fetal kidney is most commonly caused by UPJ obstruction. Although UPJ obstruction can be found in all age groups, fewer cases are discovered in older children and adults, and a crossing vessel is the more likely etiology in those cases.[20,21] Published data suggest a low incidence of crossing vessels as the etiology of UPJ obstruction in infants referred for surgical repair, in sharp contrast to a 50% incidence in patients coming to surgical repair at a later age. Before antenatal ultrasound became widely available, 25% of cases of UPJ obstruction were diagnosed before age 1 year, and 50% were diagnosed before age 5 years.[3,22]

Etiology of Obstruction

EMBRYONIC DEVELOPMENT OF THE URETER

Hydrostatic pressure is generated in the developing fetal kidney as urine accumulates between 9 and 12 weeks of gestation with subsequent distention of the developing renal pelvis. Chwalla membrane is found at the distal end of the ureteric bud, and its rupture during this period of gestation allows the accumulated urine to enter the bladder.[23] The purpose of this membrane is unclear, but during gestation it usually develops between days 35 and 37, then disappears between days 43 and 49. Chwalla membrane has been hypothesized as either a protective mechanism for excretions from the metanephros or as a temporary structure appearing as the urogenital sinus resorbs the common nephric duct.[24] The lumen of the ureter appears to fuse and become a solid cord between 28 and 35 days, during which the lumen is not apparent histologically. It then undergoes subsequent recanalization, beginning at 42 days' gestation in the middle portion of the ureter (i.e., metanephric cord), then progresses distally and proximally. The most distal portion of the UVJ and the most proximal portion of the UPJ are the last parts of the ureter to recanalize. Folds, kinks, or muscular invaginations in ureteral formation also may persist during recanalization.[13,25,26]

It is appealing to hypothesize that intrinsic UPJ obstruction may result from incomplete canalization of the proximal ureter. Whether this is a universal pattern in the mammalian kidney is uncertain, and more recent studies of ureteral development would call this into question.[27] Other possible mechanisms include obstructing valvular mucosal folds, proximal ureteral polyps, and functional abnormalities of ureteropelvic muscular contractions.[26,28-32]

Light microscopy at the obstructive UPJ shows increased collagen deposition at the proximal or distal ureter, an inflammatory cell reaction, muscular malorientation, and thickened adventitia.[10,33,34] It is unclear whether these histologic changes are the causes of, or subsequent to, obstruction. Evidence has emerged suggesting abnormal innervation of the UPJ as a basis for disordered function and obstruction.[35-39] Although this idea may be seen as a parallel of the aganglionic character of Hirschsprung disease in the gut, it is unclear which is cause or effect. Similar questions have been raised about UVJ obstruction, which may share a similar etiology. Inflammatory mechanisms also have been postulated, although whether this is cause or effect is unclear.[40]

These uncertainties are challenged further by the observed resolution of the effects of these obstructions, particularly with regard to neonatal UVJ obstruction.[41-43] Such resolution suggests a delayed maturational process. In these patients, it may be postulated that segmental peristaltic function has not matured, and the system is overwhelmed by the volume of urine output, resulting in proximal ureteral dilation. Resolution eventually comes with "catch-up" of the functional capacity of the transport system. The converse also may be seen, which may provide some insight into the underlying mechanism of obstruction. There are reports of children with mild hydronephrosis who subsequently develop marked dilation at a later age, some with symptoms. This progression would suggest a system that was an effective (although just barely) transport system up to a certain volume per unit time, but becomes dysfunctional at the higher volumes with increasing age and size of the child; this may explain cases of presumed "acquired" UPJ obstruction in children.

This delayed maturational process is not the same as intermittent obstruction, in which there is a very dynamic character to the UPJ segment that is flow dependent on an acute basis, rather than in the long-term. It also is possible that the observed resolution is due to changes in infantile bladder function that had produced upper tract dilation. Uncoordinated voiding can produce hydronephrosis, and it has been shown to occur often in infants, particularly boys.[44] This might be enough to produce mild degrees of first renal pelvic, then ureteral, dilation, which would resolve with maturation of bladder dynamics.[45] Although the fact of spontaneous resolution of congenital hydronephrosis in some children is not disputed, understanding the mechanism and predicting in whom this will occur are unclear.

ROLE OF THE RENIN-ANGIOTENSIN SYSTEM IN UNDERLYING MECHANISMS OF URETEROPELVIC JUNCTION OBSTRUCTION

Several studies have suggested a role for abnormalities in the action or expression of elements of the renin-angiotensin system (RAS) in pathologic development of the ureter.[46-50] It has been shown that ureteral function is mediated by a local RAS.[51] Various forms of ureteral pathology have been associated with absence of angiotensin receptors in rodents, including dysmotility.[48,52] Although hydronephrosis is present, and this is presumably due to an obstructive lesion, the character and severity of that lesion have not been described. Abnormal renal development has been well shown to result from abnormal expression and activity of the RAS, including impaired vasculature and structural elements.[53,54]

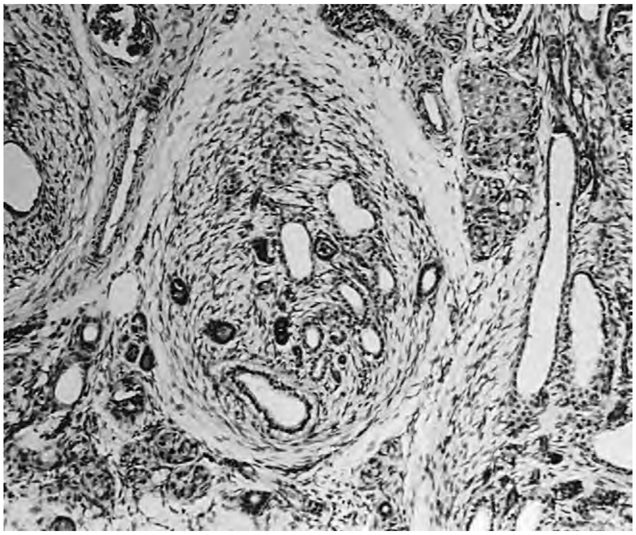

Figure 19-1 Photomicrograph of a fetal sheep kidney after unilateral ureteral obstruction at 55 days' gestation. The kidney was markedly growth impaired and irregular, and had a fibrous feel. Histology showed reduced glomerular number, disordered renal architecture, almost no medullary development, dilated tubules with primitive fibromuscular collages, and a greatly increased interstitium. (From Peters CA. Obstruction of the fetal urinary tract. *J Am Soc Nephrol.* 1997;8:658.)

Renal Pathology of Urinary Obstruction

There are few descriptions of the renal pathology of congenital upper urinary tract obstruction.[55] Many of these descriptions include the effects of a period of obstruction extending into the postnatal period. In the extremes, the patterns of histopathologic change are those of dysplasia in various degrees. Although there is debate as to the precise definition of dysplasia, it serves little purpose.[56,57] The clear observation is that these kidneys are markedly disordered in their underlying architecture. Whatever insult caused this process, it was sufficiently early to disrupt the initial patterns of nephrogenesis. It is likely that dysplasia is a group of patterns that represent the end stages of various causes, and it may not be useful to attempt to identify causes based on this late stage. There seems to be enough suggestive evidence that obstruction is the basis for some dysplasias, and even dysplasias with barely recognizable renal structure, such as multicystic dysplastic kidney, have elements suggestive of an obstructive etiology.

In the extreme, either in severity or early onset, obstructive processes can alter how the kidney develops.[58-62] Such kidneys are characterized by reduced glomerular number, interstitial fibrosis, tubular atrophy, primitive-appearing tubular structures, and occasionally metaplastic tissue, such as cartilage or hematopoietic tissue (Fig. 19-1). Lesser degrees of obstructive effect have elements of these disruptions, but have the basic architectural organization of the kidney apparent. In some, there are focal areas of apparent dysplasia, which suggests not an embryonic or inductive abnormality, but segmental effects on the developing renal parenchyma by obstruction. It is analogous to the segmental nature of reflux nephropathy.

Several reports of the histopathology of human cases of UPJ obstruction can be examined for pathophysiologic clues of obstructive nephropathy that does not completely disrupt normal nephrogenesis. Attempts have been made to correlate the histopathologic findings with clinical assessment.[63,64] The features identified were present as a spectrum and included glomerulosclerosis, interstitial fibrosis, tubular atrophy, inflammation, and medullary thinning. In most reports, no direct correlation was apparent.

More recent studies using stringent criteria for interpretation of the renal biopsy specimens noted that when the biopsy grade was in the severe range, none of the patients had normal function on clinical imaging, and most had markedly reduced relative function.[65,66] The inference was that these kidneys had little potential for improvement after corrective surgery, although that remains to be proven. In contrast, patients with normal or near-normal histopathology largely had normal function on clinical assessment. The intermediate group (grade 3), with distinct evidence of abnormal renal tissue, had clinical studies that ranged from normal to significantly reduced function. This observation raises the question as to how well imaging tests can assess the actual condition of the obstructed kidney. Although there may be heterogeneity of pathologic effect, there is a negative effect. Perhaps these patients are more at risk for a functional loss because of their obstruction, whereas patients with apparently normal histopathology have adequately compensated for the obstruction and are not at risk for functional loss. It also was shown that tubular growth and development were altered in patients with kidneys with no overt histopathologic changes, many of whom had apparently normal function on clinical imaging assessment. The incidence of interstitial fibrosis was limited to kidneys in patients older than 1 year of age, raising the question of the progressive nature of these conditions in humans (Fig. 19-2).[65]

The histopathology of obstructive uropathy raises many questions as to the mechanisms of pathologic response of the fetal kidney, but does provide clues as to the nature of the mechanisms. Obstructed kidneys are often small or growth impaired, they have evidence of changes in the pattern of development in all compartments of the nephron, and they show evidence of pathologic tissue responses including fibrosis and atrophy, although there is little inflammation in the

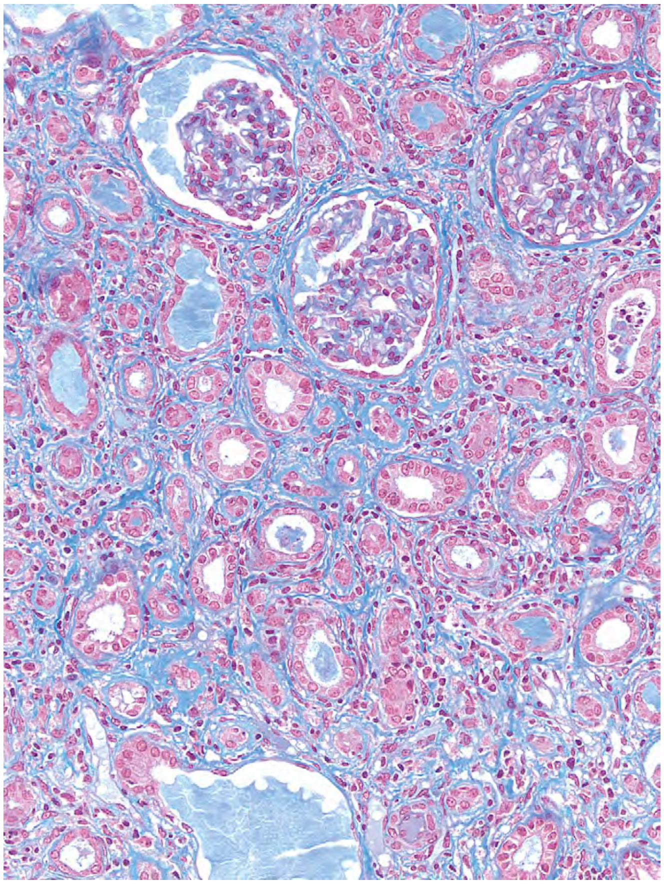

Figure 19-2 Photomicrograph of human renal tissue associated with severe unilateral ureteropelvic junction obstruction, showing marked interstitial fibrosis (Masson trichrome stain—connective tissue stains blue). (From Huang WY, Peters CA, Zurakowski D, et al. Renal biopsy in congenital ureteropelvic junction obstruction: evidence for parenchymal maldevelopment. *Kidney Int.* 2006;69:139.)

absence of prior infection. Apparent developmental impairment of specific compartments of the nephron, particularly the proximal tubules, has been reported, pointing to specific sensitivity to these pathologic changes. Other changes noted include tubular atrophy or dropout in more severe cases and occasional glomerular sclerosis and interstitial fibrosis.[65]

PATHOPHYSIOLOGIC MECHANISMS

Several components of the upper urinary tract are affected by obstruction—the collecting system, including the ureter and pelvis, and the renal parenchyma. Within the renal parenchyma, the compartments that are significantly affected can be divided into the glomerulus, including renal vascular regulation, the proximal and distal tubules, the collecting ducts, and the interstitium. Each component interacts with the others in feedback systems, and each responds to the obstruction in specific and general ways. By examining these elements, a clearer picture of obstructive pathophysiology may emerge (Fig. 19-3).

Collecting System Responses to Obstruction

The collecting system is first affected by obstruction when continued urine output distends the ureter and pelvis, increasing wall tension and producing distention. The intrinsic compliance of these structures permits maintenance of low pressures for a period of time, and the response of the smooth muscle tissues permits continued urine transport. As with any biologic system, particularly a pump, this compensatory response may permit a stable situation, determined by the degree of obstruction, the necessary urine flow, and how the tissues respond to increased tension. With progression of these responses, however, this stability is threatened, and what were initially compensatory responses may become pathologic. Excessive dilation eventually reduces peristaltic efficiency secondary to absence of ureteral wall coaptation, necessary for generation of the bolus of urine moved through peristalsis. The reduced peristaltic efficiency may not have a significant effect on pressures, but may permit continued dilation and potentially increased wall tension.[67,68] This concept is illustrated in patients with diabetes insipidus having markedly dilated ureters on the basis of high urine flow.[69] This is a relatively obstructed system, in which the pressure generally remains low because of low outflow resistance. With increased smooth muscle contractility, pressures increase, and the tissues of the pelvis and ureter respond as does any muscular system, with hypertrophy. Compliance may be reduced, and pressures increase further until, as with the obstructed bladder, the system evolves into a decompensated state.

There is little experimental evidence regarding the response of the collecting system to congenital obstruction,[70,71] although some general concepts may be drawn from the extensive literature of postnatal investigation.[72-74] Obstruction invariably induces dilation of the ureter and pelvis with associated increases in total muscle mass or cross-sectional area. There is muscle hypertrophy, and an increase in contractile force, but this is not translated into increased intraluminal pressures because of dilation of the pelvis (and Laplace's law). Transport efficiency is reduced, but pressures remain low. Alterations in the transmission of the peristaltic wave also have been shown, which may affect transport further.[75] Similar findings were observed in fetal sheep,[70,71] and have been examined in human ureteral and renal pelvic specimens.[66,76-78]

Associated with the marked increases in smooth muscle is a concomitant increase in the extracellular matrix surrounding the smooth muscle cells.[31] As in the bladder, this increase affects transmission of neuromuscular impulses and reduces tissue compliance. These changes have been shown morphometrically in a fetal sheep model and have been shown to be associated with alterations in contractility characteristics of the ureter.[70] The cellular basis of these changes may follow patterns similar to the bladder in which mechanical signals can be shown to regulate cell proliferation and the deposition and breakdown of the extracellular matrix. A local RAS seems to be a potentially important regulator of these responses, an observation that may open new avenues for therapy.[51]

The specific signals for smooth muscle proliferation may differ between the ureter/pelvis and the bladder. Experimental dilation of the bladder induces increased gene expression of the potent growth factor heparin-binding epidermal growth factor (HB-EGF),[79] which is induced by mechanical stretch within individual cells.[80-82] In the obstructed ureter, however, HB-EGF is not induced.[80] This paradox may be explained by the embryologically distinct origins for the ureter and bladder. It is also supported by the clinical observation that trabeculation as seen in the bladder does not occur in the ureter, which undergoes massive dilation and smooth muscle hypertrophy, but not trabeculation.[83] Within the bladder, the trigone does not become trabeculated; it is thought to share a common embryologic origin with the ureter. Although the patterns may be similar between bladder smooth muscle and smooth muscle of the upper urinary tract, they are distinct.[84]

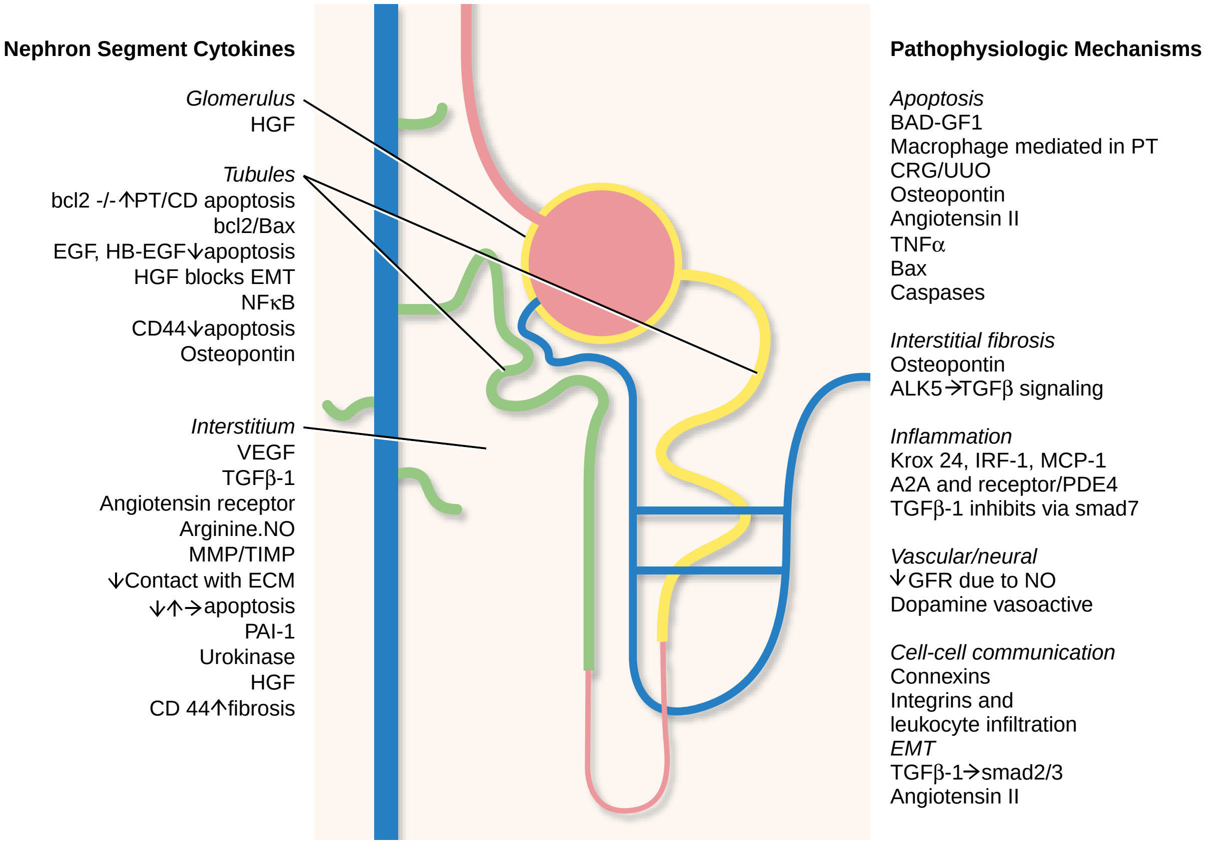
Nephron Segment Cytokines
Glomerulus
HGF
Tubules
bcl2 -/-↑PT/CD apoptosis
bcl2/Bax
EGF, HB-EGF↓apoptosis
HGF blocks EMT
NFκB
CD44↓apoptosis
Osteopontin
Interstitium
VEGF
TGFβ-1
Angiotensin receptor
Arginine.NO
MMP/TIMP
↓Contact with ECM
↓↑→apoptosis
PAI-1
Urokinase
HGF
CD 44↑fibrosis
Pathophysiologic Mechanisms
Apoptosis
BAD-GF1
Macrophage mediated in PT
CRG/UUO
Osteopontin
Angiotensin II
TNFα
Bax
Caspases
Interstitial fibrosis
Osteopontin
ALK5→TGFβ signaling
Inflammation
Krox 24, IRF-1, MCP-1
A2A and receptor/PDE4
TGFβ-1 inhibits via smad7
Vascular/neural
↓GFR due to NO
Dopamine vasoactive
Cell-cell communication
Connexins
Integrins and
leukocyte infiltration
EMT
TGFβ-1→smad2/3
Angiotensin II

Figure 19-3 Diagram of mediators of obstructive nephropathy with their site and category of action. See text for abbreviations.

Further investigation is needed to begin to understand the mechanisms of ureteral and renal pelvic response to obstructive processes.

Renal Responses to Obstruction

Throughout the evolution of an obstructive process, the kidney continues to generate urine, which may be moved through the system by filtration pressure provided by systolic blood pressure. This increase in collecting system pressure affects the renal parenchyma. The urodynamic properties of the collecting system, whether it includes the ureter and pelvis or just the pelvis, are the key determinants of what pressures the renal parenchyma is exposed to, and this is the mediator of obstructive nephropathy. The means by which that signal is passed onto the tissues of the kidney and how those tissues respond are the functional elements that must be understood.

As indicated in Figure 19-3, the renal response to obstruction may be divided into the glomerular, tubular, and interstitial responses. Each segment responds with several alterations that collectively produce the complex of obstructive nephropathy. Some of these responses are similar, but may have a distinct effect in each tissue. Overarching these segmental responses are integrative responses that remain poorly understood, including hemodynamic, hormonal, and neural factors. These factors may be influenced by the condition of the opposite kidney as well. Experimental evidence continues to develop and elucidate the specific mechanisms of renal effects of obstruction, although much of this is in postnatal systems.[9,55,85,86]

Congenital obstruction is distinct from postnatal obstruction, and caution must be exercised in extending conclusions from postnatal studies to fetal systems. Fetal filtration is provided by the placenta, and the filtration function of the fetal kidney is quite different from that of the postnatal kidney. In fetal life, the kidney receives about 5% of cardiac output, in contrast to 20% postnatally. Differences in oxygen tension, hormonal levels and sensitivity, and homeostatic mechanisms have been well documented.[87] The fetal kidney is a developing entity. Its regulatory systems are incomplete and evolving. Its capacity and patterns of response to any challenge are forming, yet this is the kidney exposed to obstruction, at the point where it has only started to develop its ability to respond to a challenge such as obstruction. The postnatal kidney has already formed much of its repertoire of responses, so experimental evidence drawn from postnatal renal responses to obstruction may not reflect fetal renal responses at all. With that caveat, and a developing body of fetal studies, however, some conclusions regarding fetal renal obstruction may be drawn.

RESPONSE PATTERNS

Three classes of response to obstruction may be identified in each of the four renal segments. Obstruction in the fetal kidney produces alterations in growth regulation, tissue differentiation, and specific injury responses. Connecting these responses are potential changes in the integrative systems of renal physiology, principally its hemodynamics and innervation. The ultimate result can be abnormal development and abnormal function. Response patterns in the developing kidney, as with many biologic systems, also can be seen as compensatory. These compensatory mechanisms may be beneficial

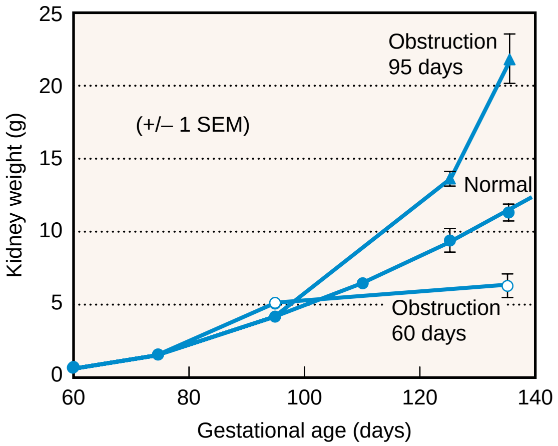

Figure 19-4 Effect of unilateral ureteral obstruction on fetal sheep renal growth. Early obstruction produces significant growth impairment, whereas later gestation obstruction induces accelerated growth. (From Peters CA. Obstruction of the fetal urinary tract. *J Am Soc Nephrol.* 1997;8:657.)

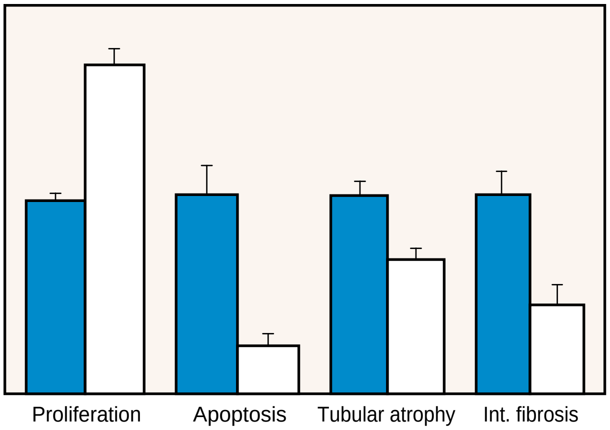

Figure 19-5 Effects of exogenous epidermal growth factor (EGF) on the renal cellular response to unilateral ureteral obstruction. After unilateral ureteral obstruction on the first day of life, rats received EGF injections, 0.1 mg/kg/day for 7 days, after which kidneys were removed for histomorphometric analysis. Shown is the relative change in the group that received EGF *(white bars)* compared with the normalized value for vehicle-treated rats *(blue bars)*. Cellular proliferation was measured by counting nuclei staining for proliferating cell nuclear antigen; apoptosis was measured using the terminal dUTP nick-end labeling (TUNEL) technique; tubular atrophy was measured by counting tubules with thickened periodic acid–Schiff–positive basement membranes; and interstitial fibrosis was measured as the areas of blue staining collagen in Masson trichrome–stained sections. Data shown as mean ± standard error of the mean; all changes were statistically significant ($P < .05$). (From Chevalier RL. Pathophysiology of obstructive nephropathy in the newborn. *Semin Nephrol.* 1998;18:590.)

initially, but also may eventually progress to being deleterious, producing a decompensated state.

Growth Regulation

Growth regulation determines the number of cells, the number of glomeruli, and the length of tubules or collecting ducts. Growth is the balance between cell proliferation and cell death (apoptosis), a tightly regulated dynamic in the developing kidney, and obstruction clearly affects this in all segments of the nephron. Fetal sheep ureteral obstruction early in gestation produces small kidneys (Fig. 19-4).[60] These kidneys are not atrophic (i.e., having lost mass), but have not grown normally. Later in gestation, this effect was much less pronounced, and with partial obstruction, kidneys were larger than normal, indicating growth acceleration. Growth regulation is complex, mediated by a multitude of growth factors that typically play specific roles at specific times in particular cells during renal development. Globally, however, growth factor expression levels are markedly higher in the early fetal kidney,[88] perhaps indicating why it seems more susceptible to growth alterations than the later gestation and postnatal kidney. Early in gestation, growth activity of the fetal kidney is extremely high relative to later in gestation. Each unit of renal mass increases its mass more quickly than it does later in gestation.

The mechanisms by which obstruction alters growth remain incompletely defined. There is some evidence that hydrostatic pressure alters cell proliferation. There are parallels in various cell types in which stretch induces growth.[81,89,90] This is seen in muscle cells as noted earlier, and in renal epithelia associated with cyst formation.[91,92] Impaired growth may be a more nonspecific effect in which markedly elevated pressures cause sufficient cell damage to reduce their ability to proliferate or may stimulate apoptotic signals and subsequent cell death.[93] Stretch may exert its growth effects by changing the balance between cell death and proliferation. In cultured renal epithelial cells exposed to severe stress, programmed cell death is induced (apoptosis).[94,95] Concurrently, there is an increase in the production of the growth factor HB-EGF. This response may be to limit cell death; when artificially expressed at high levels, HB-EGF reduced cell death in stretched renal epithelia.

As with all aspects of the spectrum of obstruction, the character of the cell, tissue, or organ response depends on the differing degrees of obstructive effect. The particular responses of renal epithelia to mechanical forces and the regulation of apoptosis may not be uniform across species, however, as reported by Kiley and colleagues,[96] who showed that EGF is a protective factor for neonatal rat renal epithelia, but is pro-apoptotic in mice. Generalizing any conclusions to humans becomes difficult.

Several experimental systems have shown obstruction to alter renal regulation of apoptosis.[96-100] Increased renal tubular apoptosis has been described in human dysplastic kidneys,[101-103] and some of the molecular signals have been defined in early neonatal ureteral obstruction.[104-107] Apoptosis is highly regulated by several proteins, including bcl-2 and clusterin. bcl-2 acts to inhibit apoptosis and is reduced in obstructed kidneys. As with most biologic systems, there is a natural balance to this, and bcl-2 is counteracted by Bax, a pro-apoptotic molecule expressed in renal epithelium. The determinants of that balance are the critical factors in the net result, not simply the expression level of bcl-2. Clusterin is a protein that acts to protect cells against apoptotic processes by maintaining normal intercellular communication. In obstructive models, clusterin is upregulated in a variable way, presumably as a response to counter apoptotic processes. In association with increased apoptosis, decreased levels of various growth factors may be seen, particularly EGF, which has been investigated in obstructive nephropathy.[98] Administration of EGF to obstructed animals has been shown to reduce apoptotic activity and reduce medullary loss (Fig. 19-5).[96,108]

Multiple factors influence the relative levels of cell proliferation and death, particularly the cellular environment. Normal connections with the interstitial cells of the kidney are necessary to prevent apoptosis in renal epithelium, a pathway mediated by nuclear factor κB (NFκB). Tumor necrosis factor-α (TNF-α) has been linked with NFκB-mediated tubular apoptosis as well, and both are related to transforming growth factor-β1 (TGF-β1) activity and apoptosis.[109,110] Local activity of the RAS modulates the level of apoptotic activity as well, acting in many systems through TGF-β1.[111] It also has been suggested that tubular apoptosis may stimulate interstitial fibrosis, the other major pathologic process in obstructive nephropathy.[112] Caspases are another important regulatory system for apoptosis in the kidney and have been shown to mediate apoptosis in mechanically deformed renal epithelia.[113]

Certain elements of the nephron seem more susceptible to obstruction. In many experimental systems, the medullary collecting ducts seem to be most severely affected.[55,60] This is often evidenced by complete loss of the medulla, while the cortex is reasonably preserved. There is no defined mechanism for this, but it is clinically corroborated by the observation of impaired concentrating ability in children with obstructive nephropathy, even without evidence of glomerular dysfunction. In unilateral conditions, this may be difficult to measure with the contralateral kidney providing effective urinary concentration. In some models, the sensitivity of particular parts of the tubular system to obstructive apoptosis is distinct[104]; this may correlate with the observation of relative proximal tubular loss in the human studies of UPJ obstruction.[65]

Increased renal mass may not be beneficial if it includes fibrotic tissues or misplaced and excessive cells. Mesangial cells (from the glomerulus) exposed to stretch proliferate, and this may produce glomerular dysfunction and sclerosis, as seen in hypertension, diabetes, and obstruction.[114,115] Several factors have been shown to mediate this response, including TGF-β1, angiotensin II, vascular endothelial growth factor (VEGF), and others. Growth regulation in both directions is crucial, and cells that do not respond to normal apoptotic signals can produce pathologic changes, including cystogenesis.[91]

A further way in which growth is altered in the kidney includes epithelial-to-mesenchymal transformation (EMT). This is a crucial developmental process by which tubular and interstitial cell populations are regulated. Although the mechanisms and signaling systems are incompletely understood, this process, when altered, can lead to significant increases in interstitial cells with subsequent functional effects. Some of the signals involved in these processes are essential early developmental pathways, including Pax2, WT-1, and the Wnt system.[116-118]

Differentiation

Development of any organ is the result of growth and differentiation; the obstructed fetal kidney may be growth impaired, but, more importantly, it may have abnormal differentiation. The regulation of cell differentiation in the fetal kidney is highly complex and only now being understood on a cellular basis.[119] Alterations in normal differentiation produce abnormal function in the postnatal kidney, and this may range from the absence of measurable function in a dysplastic kidney to minimal disturbances of function associated with subtle changes in tubular morphology or cellular function.

Controversy continues to exist regarding the relationship between obstruction and renal dysplasia; this is due in part to various definitions of renal dysplasia, which emerged from controversy regarding the etiology of abnormal kidneys associated with reflux and infection.[56] The controversy was renewed as fetal intervention for severe urinary obstruction began, with one camp arguing that dysplasia was an embryonic event resulting from abnormal renal induction and was irreversible. The opposing side contended that dysplasia was due to obstruction, and might be at least partially reversible. An ingenious experiment by Berman and Maizels[120,121] showed that ureteral obstruction in the chick embryo did not produce dysplasia based on strict histologic criteria, whereas physical disruption of the developing renal mesenchyme produced the appearance of dysplasia. Not all of the "obstructed" kidneys had hydronephrosis, however, raising the question of how effective the obstruction was.

Beck,[58] using fetal sheep, showed markedly altered renal architecture with early gestation (58 days out of 140 days) unilateral ureteral obstruction. Several investigators have reproduced these findings (see Fig. 19-1).[59,60,62] The important observation is that obstruction undoubtedly alters normal patterns of development. Whether it should be called "dysplasia," "obstructive dysplasia," or "dysgenesis" is arbitrary and perhaps irrelevant. Not all renal dysplasia is due to obstruction, but it is clear that it can be, and some of it is. In a boy with severe valves and dysplastic kidneys, one might invoke two problems (i.e., valves and embryonic dysplasia), although it seems equally likely that the renal failure is due to the obstructive process.

Alterations in renal differentiation are the result of disordered cell interactions in most cases. The process of normal nephrogenesis is a complex interplay of cell signaling, growth, death, and change. Some of the key factors in this interaction have been described, and specific alterations in their expression patterns can be induced with obstruction.[122-124] In markedly abnormal kidneys, such as multicystic dysplastic kidneys, expression patterns of key signaling molecules are disordered, such as PAX-2, an embryonically expressed protein that is critical in nephrogenesis.[102] Obstruction of fetal sheep kidneys acutely induces altered expression of several embryonic signaling molecules.[125] More prolonged postnatal obstruction in rodents undergoing nephrogenesis induced changes in a class of important renal signaling molecules, Wnt-4, Wnt-7b, and Wnt-11.[126] The pattern observed was one of abnormal persistence of expression of Wnt-4, or reactivation of Wnt-4 if obstruction was induced after the completion of nephrogenesis, suggesting induction of fetal or immature cellular signaling systems, out of the normal maturational pattern.

Although the cause-and-effect connection has yet to be proven, the association is compelling. The end result of reduced glomerular number has been shown in multiple experimental systems with early obstruction. In fetal sheep, this produced a 40% to 60% reduction in glomeruli at term with early gestation obstruction.[60] Neonatal partial obstruction in the pig produced almost 30% reduction in glomerular number with no apparent reduction in glomerular filtration rate when measured acutely.[127] In obstructed neonatal rats, glomerular reduction was proportionate to the duration of obstruction, with a 40% reduction after 5 days of obstruction.[128]

Normal patterns of nephrogenesis can be markedly disordered in the setting of obstruction. This also may lead to complete lack of glomerular development in severe cases, which would preclude further development of that nephron. Individual cells require the appropriate signals to differentiate normally to function, and if this is disordered during fetal life, postnatal function may be impaired.

Differentiation patterns of other elements of the nephron may be affected by obstruction as well. In the proximal and distal tubules, normal expression and function of ion transporters, critical to tubular function, may be disrupted by obstruction. In the collecting duct, expression of aquaporin-2 (AQP-2) is affected by postnatal obstruction, producing changes in the ability of collecting duct cells to regulate water homeostasis, and contributing to postobstructive diuresis. Permanent loss of normal aquaporin expression and regulation, as might occur with early obstruction, may be the cellular basis for the nephrogenic diabetes insipidus seen in some cases of obstructive nephropathy.[129-133] This effect has been suggested in a fetal model of vesicoureteral reflux, although not proven in a model of fetal obstruction.[134]

Part of normal renal development includes maturation of interstitial fibroblasts; some of these cells are transformed into renal epithelia in the process of nephrogenesis,[116,135] whereas others disappear. Obstruction has been shown to induce an abnormal transdifferentiation of these immature fibroblasts to myofibroblasts, which may have a significant role in production of abnormal ECM.[136,137] Myofibroblasts are typically found to express α-smooth muscle actin, which is seen to persist in neonatal obstruction beyond the time of normal disappearance.[138] Similar abnormal expression of α-smooth muscle actin has been shown in fetal renal obstruction.[139] Other markers of cellular immaturity have been shown in fetal and neonatal obstruction, such as vimentin.[140] This finding indicates not only a disruption of normal differentiation in renal interstitium and epithelium, but also a disturbance of the normal cell-to-cell signaling that regulates these cells.

Injury Responses

Alterations in growth and differentiation are important factors in the response of the fetal kidney to obstruction, but they interact with a wide variety of responses that may best be termed "injury responses," in that they are abnormal or exaggerated normal responses to a stimulus—in this case, obstruction. These injury responses have been studied largely in postnatal animals, and their relevance to fetal urinary obstruction remains uncertain. Some specific studies of fetal obstruction have been performed. These injury responses include fibrosis (scarring), inflammation, and altered cell proliferation as noted earlier.

Tissue Fibrosis

Fibrosis is a common and damaging process in the kidney and may be evident as glomerulosclerosis, interstitial fibrosis, or parenchymal scarring. It is a common final pathway of renal injury in various conditions, including diabetic nephropathy, hypertensive nephropathy, and several glomerulopathies.[141-143] Increased connective tissue has long been described in obstructed kidneys, but only more recently have the mechanisms of tissue fibrosis in obstruction been examined. Fibrosis is the result of increased net deposition of various connective tissues, including collagens, fibronectin, laminin, and many others around normal cells. The increased ECM may distort normal physical arrangements and intercellular signaling, and cause loss of function, or it may produce abnormal function itself by changing the physical properties of the tissue, as in the bladder. Recognizing the importance of intercellular communication within the kidney, it is readily apparent that disrupting the physical arrangements of the various cell types may impair function and normal developmental processes.

ECM homeostasis is a highly regulated balance of synthesis and degradation, with the latter mediated by local tissue enzymes, the matrix metalloproteinases (MMPs) (the designation as metalloproteinases reflects the presence of metallic cofactors essential for enzyme activity, usually zinc). The degradation of the ECM is itself regulated by a balance in which the activity of the MMPs is inhibited by tissue inhibitors of metalloproteinases (TIMPs). The net degradative activity (proteolytic balance) determines the rate of ECM breakdown, which in combination with even stable ECM synthesis can markedly alter the amount of ECM present in any tissue. Alterations in activity levels of the MMPs and TIMPs have been shown in numerous renal diseases associated with fibrosis, including obstruction.[117,144-146] Disruption of the proteolytic balance also has been shown in obstructed fetal kidneys (Fig. 19-6).[139,147]

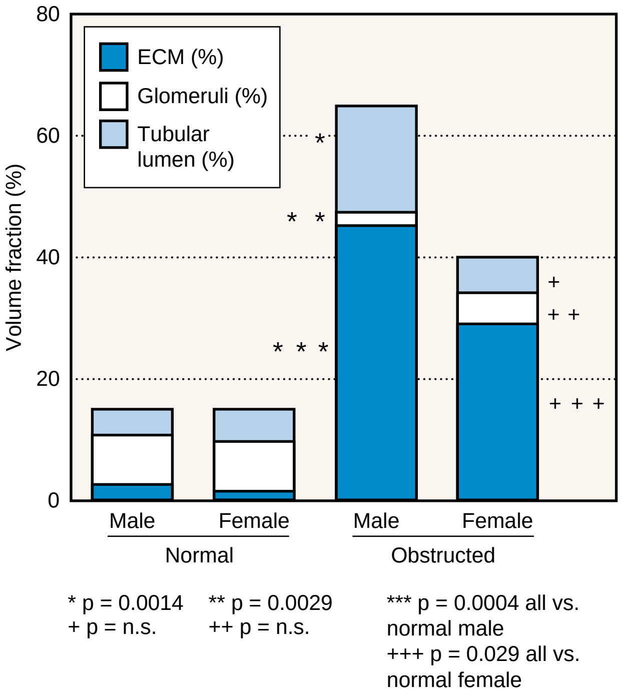

Figure 19-6 Increased tissue fibrosis is shown in response to partial fetal bladder outlet obstruction with marked increases in the extracellular matrix (ECM) compartment, and reduced glomerular volume fraction and increased tubular lumen volume fraction. (From Gobet R, Bleakley J, Cisek L, et al. Fetal partial urethral obstruction causes renal fibrosis and is associated with proteolytic imbalance. *J Urol.* 1999;162 [3 Pt 1]:858.)

Various factors alter the relative activity levels of the MMPs and TIMPs, the determinants of the renal proteolytic balance. One of the most important is the cytokine TGF-β1, which generally acts to promote fibrosis in a variety of tissue types. In diabetic and hypertensive nephropathy, TGF-β1 levels are elevated, experimentally and in humans. Pharmacologic renoprotection in diabetic glomerulosclerosis has been correlated with reduced serum TGF-β1 levels.[148] TGF-β1 is a complex growth factor, having many roles that depend on where it is expressed and what is around it; its actions are context dependent.[149] It has been recognized to be stimulated by another important renal cytokine, angiotensin II, in a variety of situations.[150-152] This relationship is emerging as a crucial one in several postnatal nephropathies, particularly hypertension and diabetes. Pharmacologic inhibition of the production or action of angiotensin II is now being explored in patients to reduce the fibrotic effects of these disease processes.[152] This effect may be mediated in part by alterations in blood pressure, but there is strong evidence that a major component of its action is independent of blood pressure reduction and reflects direct action of the renal RAS apart from the vascular system.[153,154]

This observation supports the developing understanding of the role of a local RAS within the kidney. This system acts completely within the kidney tissues, often in one compartment, and is not directly regulated by the hormonal RAS more familiar to us. Similar local RAS activity has been shown in the heart, vascular tree, and bladder. Its importance is being exploited in various disease states, including hypertrophic cardiomyopathy, with the use of pharmacologic RAS inhibitors.[155] In the kidney, this system seems to be important in glomerulosclerosis by mediating mesangial cell proliferation and fibrosis. These processes are the pathophysiologic basis of glomerulosclerosis and proteinuria. Similar alterations have been shown in the renal interstitium, producing interstitial fibrosis.[156]

TGF-β1-induced fibrosis also may be ameliorated by inhibition of its downstream signaling molecules (smad 2 and 3) using hepatocyte growth factor (HGF).[157,158] It seems likely that common patterns of injury response are induced by a variety of injuries. In the postnatal animal, obstruction has been shown to induce tissue fibrosis, mediated by TGF-β1 and activity of the RAS. The relevance of these mechanisms is supported by evidence of reduction in injury by pharmacologic inhibition of the RAS.[152] This inhibition may be achieved by blocking conversion of angiotensin I to angiotensin II (converting enzyme inhibition) using agents such as captopril, or by blocking the type 1 angiotensin II receptor, AT-1 (e.g., with losartan).

There are two principal receptors for angiotensin II with generally opposing actions. AT-1 has been linked with the vasoconstrictive action of angiotensin II, cell proliferation, and profibrotic activity. AT-2 seems to act to inhibit proliferation and fibrosis. These two receptors are developmentally regulated, and their relative abundance and their spatial distribution change during fetal life within the kidney.[159,160] The net effect of angiotensin II changes during fetal life. This observation raises another potential effect of fetal obstruction that would be distinct from postnatal obstruction because if obstruction alters the developmental regulation of these receptors, the response of the fetal kidney may be entirely different from that in postnatal life. In fetal sheep bladder outlet obstruction, the ratio of renal gene expression of AT-1 and AT-2 is altered, although the functional consequences of this remain to be defined.[161] These experiments also showed an overall activation of the RAS in fetal obstruction, paralleling the observations of Yoo and colleagues[162] in neonatal obstruction.

In a long series of experiments using neonatal animals in which nephrogenesis continued postnatally (providing a more "fetal" postnatal model), the role of the RAS in obstructive nephropathy has been explored. With obstruction, the normal maturational change in the location of expression of the renin gene was delayed, and an immature pattern was seen to persist.[163] Overall levels of expression were increased by induction of new cells to secrete renin. In an adult kidney with obstruction, renin expression is increased, but only to much lesser degrees than in neonates. Neonatal obstruction induces a downregulation of both angiotensin II receptors acutely, but with longer duration, relative levels of AT-1 are much increased over AT-2.[162]

Further confirmation of these mechanisms was found in experiments with neonatal ureteral obstruction in animals with different numbers of functional copies of the gene for angiotensinogen, the substrate for the synthesis of angiotensin II.[164] In these animals, expression of angiotensinogen gene correlated directly with the degree of interstitial fibrosis, with the least observed in animals unable to synthesize angiotensinogen. In all of these experiments, normal development of the unobstructed contralateral kidney was impaired by inhibition of RAS activity, owing to the dependence of the fetal kidney on normal levels of activity of the RAS.[165] Simple inhibition as a therapeutic tool is not likely to be effective. An understanding of the interactive mechanisms may permit selective interventions, however, in the molecular signaling patterns induced by fetal obstruction.

Immunologic and Inflammatory Responses

A consistent hallmark of postnatal obstructive nephropathy is the presence of an inflammatory infiltrate, including lymphocytes, eosinophils, and macrophages. The role of this infiltrate and the mechanisms of its occurrence have been studied extensively.[144] In the obstructed fetal kidney, however, inflammation is an unusual finding.[60] Human studies of congenital obstruction do not reveal significant inflammatory infiltrates.[65] There has been little examination of inflammatory factors in fetal obstruction, and all current information is based on acute postnatal obstructive models. Postnatally, however, the obstructed kidney often has an inflammatory infiltrate, so these processes are undoubtedly relevant to all types of obstruction. Several factors have been investigated.

Diamond and colleagues[145,166,167] examined the role of macrophages in producing interstitial fibrosis through production of TGF-β1 and other cytokines that promote fibrosis. One of the results of this process is increased activity of the TIMPs, discussed earlier, which would lead to decreased ECM degradation and increased tissue fibrosis. Critical to this model is the activity of chemoattractants that induce macrophage infiltration into the obstructed kidney. Two such factors are monocyte chemoattractant peptide-1 (MCP-1), and osteopontin, both of which are expressed at elevated levels in postnatal acute obstruction.[107,168] Reactive oxygen species also may play a role in the mediation or initiation of these processes.[169] Elements of the prostaglandin system also may play a key role in the mediation of inflammatory responses, including regulating inflammatory cell activity, oxygen metabolism, and blood flow.[170-172] The last factor reflects the complex interactions that are undoubtedly ongoing during the response of the kidney to obstruction. These integrative mechanisms are likely to play a role in modulating the specific responses discussed previously.

Integrative Responses

Hemodynamics

Vascular regulation is the key to normal renal function, and it is well recognized in adults that obstruction affects renal perfusion through several mechanisms. The classic studies of Moody and associates[173-175] showed an initial increase in renal blood flow with complete unilateral ureteral obstruction and subsequent progressive diminution over time. The mediators of these changes are several, and include the prostaglandin system, nitric oxide (NO), and others. Although these elements may have a role in fetal obstruction, complete obstruction is rare, and usually associated with a severely dysplastic kidney.

The fetal kidney is a vascular organ, and obstruction is certain to play a role in vascular regulation. Few investigators have examined this aspect of fetal obstruction. More recent studies by Mure and coworkers[176] have shown that with complete fetal obstruction, renal perfusion declines in proportion to parenchymal loss. In partial obstruction, however, Bogaert and associates[177,178] reported that despite several weeks of partial unilateral ureteral obstruction, renal blood flow was preserved, as indexed to renal weight. Bogaert and associates[179] also have shown that NO may be an important modulator of renal vascular function in the fetal kidney. In many systems, NO is paired with and balanced against the activity of angiotensin II, further developing the role of renal angiotensin II in normal and pathologic renal development discussed earlier.[180-183] Each of these factors may be manipulated pharmacologically.

Renal Innervation

Renal nerves are a neglected component of renal physiology, perhaps because of the difficulty in studying their function, but there is strong evidence that they play major roles in various renal functions. There is evidence of their modulation by obstruction in the regulation of renin expression in the neonatal obstructed kidney,[184] and the hemodynamic response to obstruction. It also is possible that renal innervation is crucial in the crosstalk that occurs between the two renal units. In nearly all experimental models of unilateral obstruction, the contralateral kidney shows evidence of change. In fetal life, this change has been shown by contralateral compensatory hypertrophy with unilateral early gestation obstruction.[185] It also is suggested by observations that the response of a kidney to obstruction depends on the condition of the other kidney. When both kidneys are obstructed, the kidneys are more likely to be hydronephrotic, rather than cystic or dysplastic. A solitary obstructed kidney acts as bilaterally obstructed kidneys.[60] Renal innervation may play a role in this crosstalk, and potentially modulate individual renal responses to obstruction.

FUNCTIONAL EFFECTS

The end result of disordered growth, differentiation, and injury response is abnormal function; there is a wide spectrum of functional impairment. Function also must be seen in a time scale because renal disease may be progressive. Progression of renal disease may occur after the initial insult has been removed, owing to loss of functional renal mass or owing to ongoing injury response such as fibrosis. No studies of fetal obstruction have examined postnatal function over time.

Several models of chronic obstruction in fetal sheep have examined renal function in utero. Glick's study[186] of in utero severe UPJ obstruction examined prenatal function, and determined that obstructed kidneys were markedly impaired in terms of glomerular filtration rate and sodium handling (increased fractional excretion of sodium) compared with controls. Histologically, these kidneys were significantly abnormal with diffuse structural changes, despite in utero decompression.[186,187] In a model of fetal obstruction with decompression in utero, Ward and coworkers[188] reported reduced creatinine clearance and higher fractional excretion of sodium. With varying degrees of obstructive severity, Peters and colleagues[60] identified increased sodium clearance and reduced free water clearance in more severe obstruction. Bussieres and associates[189] used a model of partial bladder outlet obstruction and assessed creatinine clearance in utero. They reported reduced clearance depending on the onset of obstruction. In contrast, Bogaert and colleagues[178] found no change in renal function with partial bladder outlet obstruction in utero. It is difficult to assess the significance of these data with respect to postnatal function because of the low level of normal clearance present in the fetus, the lack of standardization of the severity of obstruction, and the absence of postnatal functional evaluation.

In the pouch ("fetal") opossum, ureteral obstruction produced marked reduction in creatinine clearance when examined at adulthood, even when unobstructed at full term. Several animals had only partial obstruction and hydronephrosis, but had minimal reduction in clearance associated with significant reduction in renal weight.[190]

There are several congenital models of apparent ureteral obstruction described in rodents. Boineau and colleagues[191] reported on a rat with unilateral hydronephrosis consistent with a UPJ obstruction. This animal showed reductions in glomerular filtration rate 25% below normal, which were angiotensin II and thromboxane A_2 dependent. The structural nature of the lesion has not been defined, however, and pressure-perfusion studies failed to show significant increases in pressure despite extremely high flow.[192] It may be that even with a mild obstructive effect, it is possible to have significant functional loss. Alternatively, it is possible that this is not an obstructive process, but one of renal maldevelopment, creating the appearance of hydronephrosis owing to a relative absence of the medulla.

Other models have been reported with similar findings, created by genetically or pharmacologically knocking out elements of the RAS,[100,193,194] although at relatively low frequency. The RAS plays a crucial role in normal renal development, and without it, parts of the kidney simply do not develop. This may lead to a small kidney, but also may produce an appearance of hydronephrosis. In a comparison between normal animals undergoing complete unilateral ureteral obstruction and animals lacking the angiotensin II receptor (AT-1), Miyazaki and coworkers[195] showed nearly identical morphologic results with dilated calyces and atrophic papillae. They also showed that the knockout animals had deficient renal pelvic and ureteral peristalsis, and found elevated intrapelvic pressures in the unoperated but hydronephrotic mutant animals compared with normals, findings that also have been linked to calcineurin knockouts. No specific point of obstruction was located in the hydronephrotic animals.

These results indicate the potential for a molecular basis of the ureteral dysfunction, but also may suggest that the appearance of hydronephrosis may be the result of a growth disturbance not mediated by physical obstruction. The same group has reported on various congenital uropathies associated with different mutations in the RAS. Although these are compelling observations supporting the role of the RAS, they do not yet prove the underlying etiology, but may be a "downstream" mimic of secondarily disordered activity of the RAS from obstruction. These models provide powerful tools for further study.[49]

Many postnatal models of ureteral obstruction have been reported with a wide range in structural, functional, and temporal effects. In part, this wide range is due to the means of creating obstruction. Complete obstruction is uniformly associated with progressive irreversible loss of all aspects of renal function, and yet is rarely encountered clinically. Partial obstruction comes in a wide range of severity, so no one model is going to reflect that spectrum entirely.

Josephson and colleagues[196-201] have explored many aspects of neonatal ureteral obstruction by burying the ureter in the psoas muscle,[202] contending that this would grow with the animal, in contrast to an artificial constrictor, which would become progressively more obstructive with growth. The latter system has been used by Chevalier and colleagues[96,203-207] in the neonatal guinea pig, rat, and mouse. Both systems are appropriate, but it is unknown which patients may be represented by which model. Josephson and colleagues[200] showed apparently stable global function in the face of obstruction with long-term follow-up at maturity, in which glomerular filtration rate was 43% lower than the contralateral side. The reduction in glomerular number was about 20% with an associated increase in glomerular density,[200] as has been shown in human biopsy studies.[65] The evidence of functional stability and contralateral compensation led the authors to conclude that this model represented most human patients, and the "results do not support any rationale for early correction."[208]

In contrast, a similar model in neonatal rats was reported as having glomerular filtration rate reductions of 60% in the obstructed kidney after 1 year, which had been only minimal at short-term examination, indicating the potential progressive nature of these conditions.[209] Taki and coworkers[210] showed marked decreases in function in a short time with more severe partial obstruction produced by a Silastic cuff around the ureter. Similarly, Chevalier and colleagues[207,211,212] showed significant reductions in renal growth, development, and function with partial neonatal obstructions. Studies in neonatal partial ureteral obstruction in pigs have shown similar evidence of progressive loss of function and glomerular loss.[127,213,214]

Taken together, these investigations reflect the natural spectrum of disease seen in humans and indicate that although some degrees of obstruction produce limited functional loss, and may be stable over time, there is the potential for severe progressive functional loss. From this perspective, it would seem as if obstruction should be considered a potential threat to normal renal functional development and managed accordingly. This does not mean surgical intervention for all, but for some. The difficulty remains in determining which patient would benefit.

RECOVERY OF FUNCTION

A significant challenge in obstructive nephropathy is predicting the functional reversibility of an obstructive lesion. If differentiation has been disordered, can any functional recovery be possible? It is unknown how much of the "dysplastic" change induced by congenital obstruction might be altered with relief of obstruction. This would require a realignment of the differentiation process that has been disordered. Although some element of further normal development may occur after relief of obstruction in fetal or neonatal life, several studies have shown this to depend on the duration of obstruction.[187,215]

In a model of neonatal ureteral obstruction and decompression in the rodent, Chevalier and colleagues[215] showed apparent functional recovery associated with the presence of ongoing hyperfiltration injury and later functional loss. Even with a 40% persistent reduction in glomerular number with unilateral obstruction, overall glomerular filtration rate was maintained, confirming compensatory hyperfiltration. This finding raises the concern of the real functional severity of the obstructive renal injury, relative to what is measured, and the potential for slowly progressive injury undetected by conventional methods.[215] With variable partial obstruction, reversibility is determined by obstructive severity and duration.[207] Similar clinical findings have been reported as well when correction is delayed.[216]

Indicators of potential reversibility continue to be sought. Most of these use filtered or secreted compounds in the urine that may reflect renal glomerular or tubular function.[217,218] There has been variable success in predicting the level of functional reserve, and this may reflect simply a lack of correlation or perhaps the presence of biphasic patterns of these markers in the urine of obstructed kidneys. With progression of renal impairment, the levels of any markers may initially rise and then decline. Any given level may be on either side of the peak and reflect either worsening injury or failing of the kidney, each with a different recovery potential. With the emergence of technologies to analyze the urinary proteome, new optimism is present that clinically useful indicators of progressive obstructive uropathy may be identified.

More recent reports suggest the utility of a fingerprint-type approach in which the specific identity of the biomarkers is less relevant than the pattern that is unique to significant obstruction.[219] This study showed a very high prediction of unilateral obstructions that required surgery. These were largely very severe cases that would not be controversial. The real challenge would be to identify the patient whose obstruction would cause a slow progression but who is currently functioning well. An alternative strategy in proteomics is to use this technology to identify molecules that are altered in the face of obstruction because they are mechanistically involved in the progression of disease. These specific molecules might provide insight into the pathophysiology of the condition and permit novel therapies.[220]

CLINICAL APPLICATIONS

Although a practical understanding of the pathophysiology of congenital obstructive uropathy eludes us for now, with improved understanding of the critical elements of this condition, we will be able to manage our patients better. This improved management will come in diagnosis, prognosis, and treatment. At present, one of our greatest diagnostic frustrations is an asymptomatic child with prenatally detected hydronephrosis and apparently normal function on renal scan. Is this child at risk for functional loss? Is there already some functional loss that is not being detected on current studies? Markers of obstructive nephropathy, based on the pathophysiologic mechanisms, may help us determine this. TGF-β1, implicated in renal fibrosis and obstruction, is elevated above normal values in the urine of children with UPJ obstruction, but not correlated with long-term outcomes.[221] Similarly, *N*-acetyl-β-glucosaminidase (NAG), an indicator of tubular injury, has been shown to be elevated in UPJ obstruction, but long-term functional correlates remain to be performed.[218] Other markers may present themselves as we learn more about the response of the fetal kidney to obstruction.

As with diagnosis, prognosis is determined by ongoing response and should be able to be indicated by assessing the pathophysiologic mechanisms of obstruction. Finally, our therapy for obstructive uropathy will be improved by understanding the pathophysiology of obstruction in ways that are just emerging in medical technology. Locally delivered gene therapy to alter specific molecular processes ultimately may permit inhibition or reversal of pathologic responses in the obstructed kidney.[109,222,223] Introduction of EGF to obstructed animals has been reported to reduce the histologic effects of obstruction.[98,108] Induction of local expression of aquaporins in the tubules of the kidney may permit normalization of water metabolism in the previously obstructed kidney.

At present, an opportunity for enhanced treatment is available through the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.[153,224,225] Although this treatment may not be applicable in neonatal life, inhibition of one of the key factors in several aspects of obstructive renal pathology may provide for less renal injury and longer functional life of the obstructed kidney in an older child. Angiotensin-converting enzyme inhibitors are being used for patients with diabetic and hypertensive nephropathy, and perhaps should be explored for obstructive nephropathy.[148] Gene therapy with antisense genetic segments for AT1 have been shown to protect against cardiac hypertrophy in hypertensive rodents.[226]

Obstructive uropathy in a child is a complex, dynamic process involving a wide variety of embryonic and developmental regulators of cellular function, growth, differentiation, and communication, which produces a wide spectrum of pathology that we deal with daily. Understanding those mechanisms is essential to permit any advancement in the clinical management of the many children with these conditions.

REFERENCES

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CHAPTER 20

URETEROPELVIC JUNCTION ANOMALIES: CONGENITAL URETEROPELVIC JUNCTION PROBLEMS IN CHILDREN

Bernard M. Churchill and Waldo C. Feng

The study of pediatric hydronephrosis is important because it is a common, complicated, controversial, and challenging disease of childhood. With the increased widespread use of high-resolution real-time fetal ultrasound scans, antenatal hydronephrosis and minor dilation of the urinary upper tracts are being detected with increasing frequency.[1,2] Some studies contend that the prevalence of antenatal hydronephrosis is 0.2% to 2% of all pregnancies.[3,4]

Neonatal and infantile hydronephrosis is complex for a variety of reasons. First, neonatal renal physiology is rapidly changing with respect to increased glomerular filtration rate (GFR), increased concentrating ability, and changes in renal circulation. Second, the start of eating changes the level of nitrogenous wastes to be excreted. Third, the kidney has a unique circulation of two capillary and arteriolar beds. Differential vasoconstriction of these two arteriolar beds allows the kidney to maintain circulation, GFR, and urine formation in the presence of severe ureteral transport impairment. Lastly, much experimental data have been in models with complete ureteral obstruction versus ureteral transport inefficiency, which better represents chronic hydronephrosis.

Controversies also exist because various new technologies were described simultaneously. These technologies include diuretic nuclear renography, differential renal scans, pressure perfusion studies, resistive index studies, ultrasonography, and computed tomography (CT). Few correlation studies have been done. The published studies have shown poor correlation between these technologies and disagreement as to what constitutes the "gold standard."

The challenge for the clinician in the management of hydronephrosis is to decide which patients should be observed, which should be medically managed, and which require surgery. This decision is complicated further by the challenge of cost containment and lack of long-term follow-up studies with respect to arbitrary third-party reassignment of patients in today's health care system.

The final challenge is not to oversimplify. Many more recent articles have indicated that the greatest clinical challenge is to define "obstruction," and then to decide which cases are "obstructed" and warrant surgical intervention, and which are "nonobstructed" and are optimally managed by serial observations. Although this approach is theoretically commendable, we believe it incorrectly focuses a complex practical problem on a semantic "either/or" definition. This approach has analogies in other fields, such as "benign/malignant" in oncology. This oversimplification ignores numerous biologic, mechanical, and clinical factors. The ureter is not a rigid passive conduit similar to a pipe with a proximal compressor pumping fluid through it. Instead, it is a hollow fluid transport system that *actively* propels the urine by a series of coordinated compressing peristaltic movements of the muscular wall. Similar to any other fluid system, its transport efficiency can be defined only in terms of workload required and delivered at a particular time. This term is expressed by urine flow rate and distal intravesical pressure, both of which vary constantly in a dynamic fashion.

Many experimental models are based on a complete occlusion (via constricting ligature) system. A comparative situation occurs in pediatric urology with ureteral atresia and resultant multicystic dysplastic kidney. Universal agreement exists that these two situations represent complete ureteral obstruction. We believe the term *complete ureteral obstruction* should be restricted to these situations. In clinical cases of pediatric hydronephrosis, there is always a patent lumen, and *complete ureteropelvic obstruction does not exist*. In that situation, we prefer the term *ureteropelvic urine transport inefficiency*. We believe that the ureteral "transport inefficiencies" represent a continuous spectrum of severity, rather than two arbitrary categories. We and others have seen cases improve spontaneously and unpredictably decompensate. The severity of hydronephrosis for an individual patient is often dynamic rather than static.

Evidence strongly suggests that although measurement of (1) differential renal function, (2) renal parenchymal volume, (3) degree of dilation, and (4) ureteropelvic physiology is extremely important, these measures often do not correlate well with each other. These measurements all are used to predict the child's future, however. They attempt to answer the following questions:

1. Will the child experience further progressive irreversible loss of renal function?
2. Will the child experience further progressive loss of renal parenchymal volume?
3. Will future complications of pyelonephritis, stones, or hypertension occur?
4. Will the child develop pain or hematuria in the decades to come?
5. If renal function is currently diminished, will it improve, remain static, or deteriorate?

Although current status is useful to predict the future, it is far from infallible. Aggressive proponents of a particular testing system or strategy of management also are wise to remember that there is a major difference between established current political consensus and determining long-term scientific validity.

HISTORICAL PAPERS

The basic definition, accurate gross pathology, and fundamental pathophysiology of hydronephrosis were published well before 1935. Particularly noteworthy are the fundamental writings of Rayer,[5] whose "*Traité des Maladies des reins,*" was published in Paris in 1837. Rayer[5] noted and illustrated the following pathologic features of hydronephrosis:

1. "Retention of urine in the renal pelvis and calyces"
2. "Atrophy of the kidney" and the "cortex and kidney become smaller and sometimes completely disappear"
3. "In some cases there is a 'small opening of the ureteropelvic junction'"
4. "Hydronephrosis can be due to obstructive or micturition disorders"

In 1899, Albarran[6] described the phenomenon of "*L' hypertrophic compensatrice en pathologic rénale*." In 1907, Broedel's drawings accurately depicted the following progressive changes in hydronephrosis of increasing severity (Fig. 20-1):

1. Progressive increase in volume of renal pelvis
2. Progressive changes in shape of renal calyces from normal appearance to clubbed, to flattening, to disappearance
3. Progressive thinning of renal parenchyma

FUNDAMENTAL PATHOPHYSIOLOGY

Hinman's series of elegant papers[7-16] on experimental hydronephrotic studies in various animal models are probably the most important publications in understanding of the pathogenesis of hydronephrosis. His 1919 paper involved a rat model with unilateral ureteral ligation of variable duration, and deligation followed by ipsilateral ureterocystostomy (of ligated ureter), followed by immediate or delayed contralateral nephrectomy. Ligation of 2 weeks' duration resulted in return of most of the function to the previously obstructed kidney. Ligation of 3 weeks' duration resulted in return of 50% of renal function. With ligation duration of more than 3 weeks, the animals survived only with delayed or partial contralateral nephrectomy. Hinman's studies showed that the duration of complete ureteral obstruction significantly affects the severity and reversibility of renal damage. In 1922, Hinman also showed that infection in addition to obstruction caused more severe and rapid kidney damage than obstruction alone. In 1925, he added that "after complete ureteral obstruction in rabbits, there is progressive development of hydronephrosis" and the "degree of hydronephrotic atrophy is uniformly proportional to the duration of the obstruction."[11]

In 1925, Hinman[12] showed that partially obstructing the renal artery by a rubber band combined with ureteral ligation produced more severe and rapid renal deterioration than ligation alone. He concluded that "anemia" and "nutritional factor" resulted in "parenchymal degeneration." Hinman's son reviewed his work 38 years later and concluded that the "rate and degree of hydronephrotic atrophy" is "closely linked with the nutrition of the tissue."[16]

Hinman[12] also studied the blood supply in his hydronephrotic model by a series of postmortem barium sulfate angiograms in normal and progressively more severe contralateral

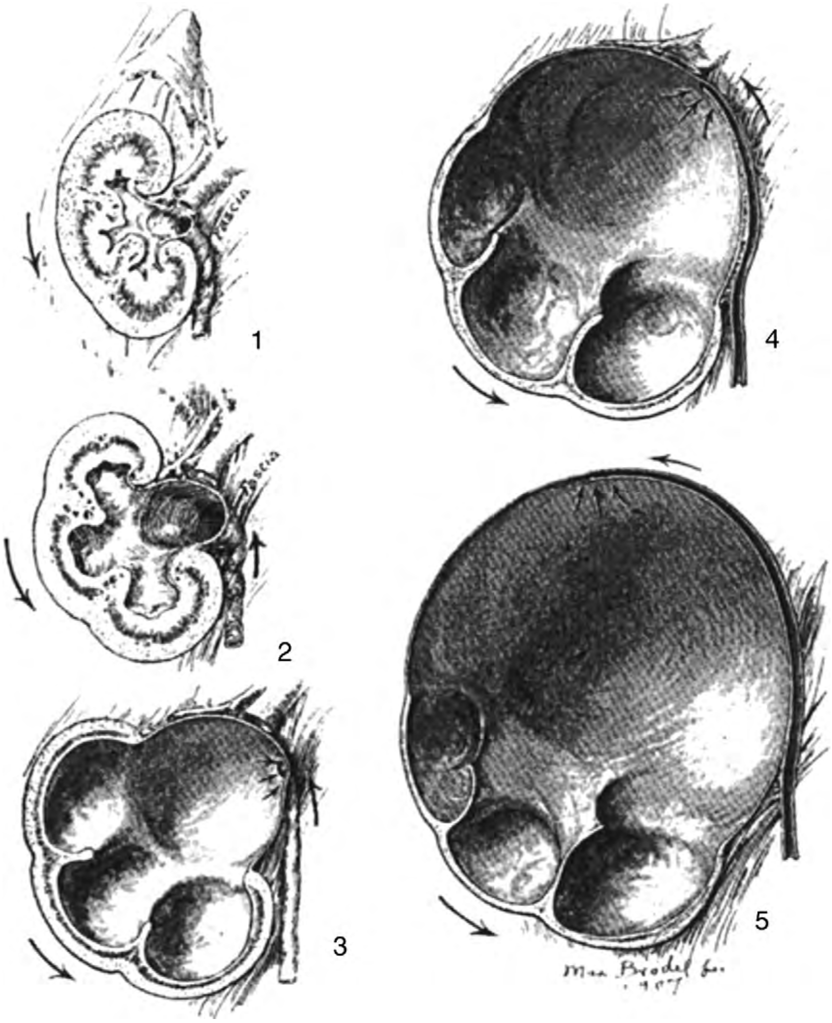


Figure 20-1 Broedel's drawings depict progressive hydronephrosis of increasing severity, including (1) increases in the size of the renal pelvis, (2) changes in the calyceal architecture, and (3) progressive renal atrophy. (From Geraghty JT, Frontz WA. A study of primary hydronephrosis. *J Urol.* 1918;2:161-188. Reprinted in *Urol Clin North Am.* 1998;25:164.)

hydronephrotic kidneys. These images revealed a "progressive thinning of the arterial tree," and elongation and narrowing of individual renal arterial branches. All of these studies confirmed the role of ischemia in hydronephrotic renal atrophy. Hinman also introduced the concept that "proportion of renal mass to the body weight is very uniform for animals of the same species." He proposed a ratio of 9.1 g of renal tissue per kilogram of body weight in cats and 7 g/kg in dogs.

In 1922, Hinman[7] stated "that the continual formation of urine after ureteral obstruction even when complete is essential to the production of hydronephrotic atrophy is self-evident." In other words, even with complete obstruction, urine continues to be delivered from nephrons to the collecting system and then reabsorbed by various mechanisms. In 1929, Morrison[17] provided experimental confirmation of continued urine formation and reabsorption by dye studies.

Finally, Hinman[13] reviewed a compensatory physiologic mechanism that he labeled "renal reserve power." This concept had several factors. First, normal animals had more renal function than necessary for survival. This was first shown by De Paoli,[17a] who performed total nephrectomy on one side and partial nephrectomy on the other side and had animals survive. Also, Hinman's review included the thesis that remaining residual renal tissue could enlarge and increase function.

EVOLVING SURGICAL TECHNIQUES

After Hinman's classic papers and before the advent of ultrasonography, the most important papers dealt primarily with innovative surgical techniques, presenting symptoms and prognostic factors in pediatric ureteropelvic junction (UPJ) problems. These included the pyeloplasty of Foley,[18] the spiral flap variation of Culp and DeWeerd[19] and Scardino and Prince,[20] and the dismembered technique of Anderson and Hynes.[21] Williams and Kenawi[22] described prognostic factors.

DEVELOPMENT OF ULTRASONOGRAPHY

The modern history of hydronephrosis is dominated by one development, maternal ultrasonography, which allowed safe detection of antenatal hydronephrosis. Before this technologic advance, congenital hydronephrosis presented throughout childhood (and adulthood) with various symptoms, including flank pain, recurrent febrile urinary tract infections, abdominal mass, urolithiasis, and hematuria. Today, most children do not present with these sequelae of long-standing chronic ureteral transport inefficiency, for which treatment is more clearly defined. Instead, most children with antenatal hydronephrosis are evaluated much earlier in the clinical course of the disease. In much the same way that prostatic-specific antigen has dramatically changed the clinical management of prostate cancer through earlier detection in clinically asymptomatic patients, a concept known as "lead time," the widespread use of ultrasound resulted in earlier detection of asymptomatic children.

The consequences of lead-time detection of hydronephrosis are far-reaching. The numbers of children with postnatal hydronephrosis have dramatically increased in parallel with the increased application of ultrasound. More importantly, the natural history of the hydronephrotic kidney has now come under question. Whether hydronephrosis represents a natural state in the dynamic development of the newborn genitourinary tract, "transitional hydronephrosis,"[23] or is the result of the underlying pathologic disease process (e.g., UPJ obstruction, vesicoureteral reflux [VUR]) has become more difficult to distinguish in the newborn. Considerable debate has arisen regarding the significance of hydronephrosis, and the timing and even the *necessity* for treatment. The diverse treatment options themselves (e.g., observation, pharmacologic management, nonoperative mechanical measures, and surgery) for asymptomatic patients continue to be controversial.

INCIDENCE

We reviewed the available literature in an attempt to appreciate the scope of the prevalence of pediatric hydronephrosis in the United States. Our findings should be viewed in the context that they are predominantly derived from single institutional data, retrospective studies, and flaws associated with meta-analysis. Certain patterns emerge, however, which are consistent among various studies.

As of the 1996 census data from the National Center of Health, there were more than 600,000 maternal ultrasound scans performed each year in the United States.[24] "Suspected antenatal hydronephrosis" is found in 0.2% to 2% of all maternal ultrasound scans; this leads to a detection rate of approximately 1200 to 12,000 new cases of suspected antenatal hydronephrosis each year. The false-positive detection rate is reported to be 9% to 22%.[25] Various series have shown that approximately 66% to 75% of postpartum ultrasound studies confirm antenatally detected hydronephrosis. We have not included cases of ultrasound-detected hydronephrosis that were not found prenatally or cases in newborns who were normal in the immediate postpartum period, but subsequently were found to have hydronephrosis as an infant.

Of patients in whom hydronephrosis persisted in the postpartum period, the most common immediate radiologic investigations obtained were voiding cystourethrogram (VCUG) and nuclear renography. In a study by Gunn and colleagues,[1] 23 of 40 (57%) infants with significant upper tract dilation were shown to have a hypoplastic adynamic segment by nuclear renography. This is the most common cause of dilation of the upper tract, accounting for nearly 60% to 80% of all persistent hydronephrosis.[26] In a follow-up series by Morin and associates,[3] 23 of 63 (36%) patients with antenatally and postnatally detected hydronephrosis had abnormal VCUGs. VUR as an etiology of hydronephrosis accounts for 25% to 35% of postnatally diagnosed hydronephrosis.[27]

UPJ problems occur most commonly in boys[28,29] especially in the newborn period, when the ratio exceeds 2:1.[30,31] Left-sided lesions predominate, and in neonates more than two thirds occur on this side. Bilateral UPJ obstruction is present in 10% to 40% of cases.[32,33] In our experience, most bilateral cases are asymmetric with one side being more severe than the other. The great variation in incidence is probably explained by variable criteria of diagnosis on the less severe side.

In this age of routine prenatal ultrasound, the study by Thomas[34] is particularly practical. This study showed the incidence of detectable in utero dilation to be 1 in 60 pregnancies, with 1 in 500 having a significant urologic problem, of which about half are problems with ureteropelvic urine transport inefficiency (Fig. 20-2).

EMBRYOLOGY

Life begins as a single cell. This cell quickly forms a basketball-shaped sphere called a blastocyst. Gastrulation (ingrowth of tissue) results in two cavities (amniotic sac and yolk sac) and a suspended disc, which becomes the future embryo. Three layers are quickly formed in the embryo—an outer ectoderm, a middle

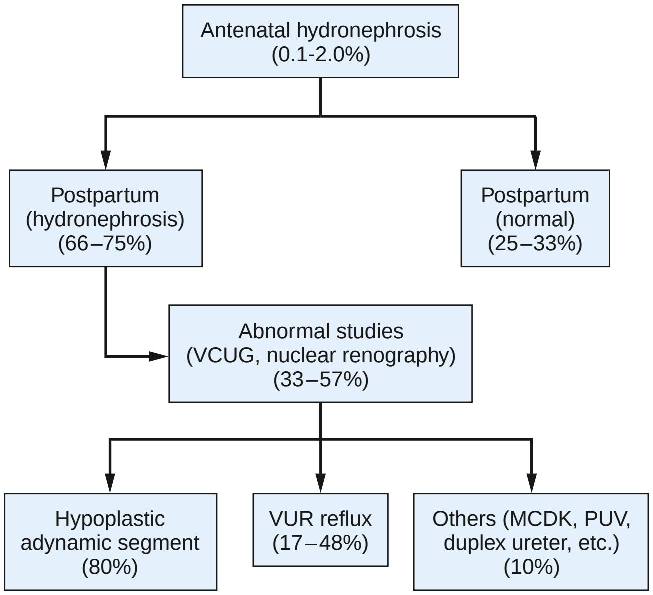


Figure 20-2 Incidence of antenatal hydronephrosis, results of postnatal studies, and causes. MCDK, multicystic dysplastic kidney; PUV, posterior urethral valves; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

mesoderm, and an inner endoderm. The endoderm forms the lining of the subsequent inner system, which later communicates directly with the atmosphere (e.g., gastrointestinal tract, respiratory tract, urinary tract, and female genital tract).

By 4 weeks of gestation, primitive organs called primordia have been formed. These include the cloaca (from endodermal tissue) and mesonephros (from mesoderm tissue). At 4 weeks, the ureteral bud forms as an outpouching of the mesonephric duct just before it joins the cloaca. The ureteral bud grows in a cranial direction and penetrates the metanephric blastomere. An important process of induction occurs at this point. Induction indicates that adjacent tissues influence each other—development of a "biochemical crosstalk." The ureteral bud induces the metanephric blastomere to transform it from an indifferent mesenchyme to form the specialized nephrons. By progressive generations of dichotomous division, the ureteral bud is induced to form the ureteral pelvis, calyces, and collecting tubules. At about 6 weeks, the midureter is a solid cord that recanalizes in both directions.[35]

Some authors have suggested that the ureteropelvic and ureterovesical areas are the last to recanalize. By this theory, Chwalla membrane may play a role because most ureteral hypoplastic adynamic segments occur at these two sites.[36] Other authors indicate this solid cord recanalization process does not involve ureteropelvic areas.[37] A more plausible explanation is that in human fetuses histologic differentiation of ureteral mural smooth muscle begins at the bladder and proceeds toward the kidney where such muscle is evident by 16 weeks of gestation. It is logical to us that premature arrest of ureteral wall musculature development leads to an aperistaltic hypoplastic ureteral adynamic segment at the UPJ region.

By the 10th to the 12th week of gestation, urine can pass from the glomerulus to the urinary bladder. By the 14th week, the ambiguous kidneys are capable of concentrating urea and removing sodium. By the 18th week of gestation, virtually all of the amniotic fluid is made of fetal urine. Most prenatal ultrasound protocols begin surveillance just before the midpoint of gestation (16 to 20 weeks), which corresponds to these developmental milestones.

PERTINENT BIOPHYSICS, PHYSIOLOGY, AND PATHOPHYSIOLOGY

Hydronephrosis associated with a congenital UPJ problem is not simply a "black or white," "obstructed or nonobstructed," problem. Rather, it is a dynamic interplay between formation of urine by the kidney, storage of urine by the renal pelvis, and transport of urine by the ureter. Also, this interplay is not static. The workload of the kidney varies according to the stages of development, maturation, growth, and varying physiologic circumstances (e.g., state of hydration and bladder pressure). To maintain homeostasis, the kidney has to excrete urine at varying flow rates. The ureter also has to be able to transport urine at varying flow rates.

"Branching" is one of the most universal of all biologic structural themes. Much of life is organized like a tree (*arbor vitae,* the "tree of life"). The kidney (such as one removed for transplantation) involves two "trees of life" in a semirigid capsule. The first is the renal vasculature with its dual trunks of the main stem renal vessels and its peripheral branches of glomerular and peritubular capillaries. The second is the urinary system with the ureters forming the analogous ureteral trunk and peripheral branches of nephrons. Inefficiency in the urinary tract leads to compulsory compensatory changes in both "trees" and possibly, if these are overwhelmed, damages or destroys the entire system. This kind of combined analysis has been uncommon; this is emphasized by the fact that pressures in renovascular physiology are measured in millimeters of mercury (mm Hg), and pressures in the upper urinary system are measured in centimeters of water (cm H_2O). Mercury has 13.6 times the specific gravity of water, and 136 cm H_2O pressure equals 100 mm Hg pressure.

There are basically four forces driving ultrafiltrate or fluid that becomes urine. These include the pressures generated in three biologic compressors: the heart, the contracting ureteral bolus, and the detrusor. Also in the upright position, gravity is a driving force. From these three biologic compressors, urine is pumped to three low-pressure containers: the renal pelvis, the bladder, and the atmosphere. We have previously proposed the concept of three serial "biohydraulic circuits" named for the compressors and the low-pressure reservoirs: cardiopelvic, ureteral-detrusor, and detrusor-atmospheric. Figure 20-3 depicts pressure along the vertical axis and measured various sites along the urinary tract.

FUNDAMENTAL BIOPHYSICS

All of these systems basically involve flow of fluid through biologic conduits and storage in vesicoelastic containers. These are biohydraulic systems. Many infallible hydraulic laws are applicable to all hydraulic systems, including the following laws: Poiseuille's, LaPlace's, the first law of thermodynamics (conservation of mass and energy), and the concepts of power/work as applied to a hydraulic system such as the upper urinary collecting system. The major determinants governing flow of fluids through hollow conduits and their interrelationship were described in a mathematical expression by Poiseuille, an 18th century French physician:

$$\text{Flow} = \frac{\Delta P \Pi r^4}{8n1}$$

Flow in a conduit is directly proportional to the change in pressure (entrance minus exit) and the fourth power of the radius, while inversely proportional to the viscosity of

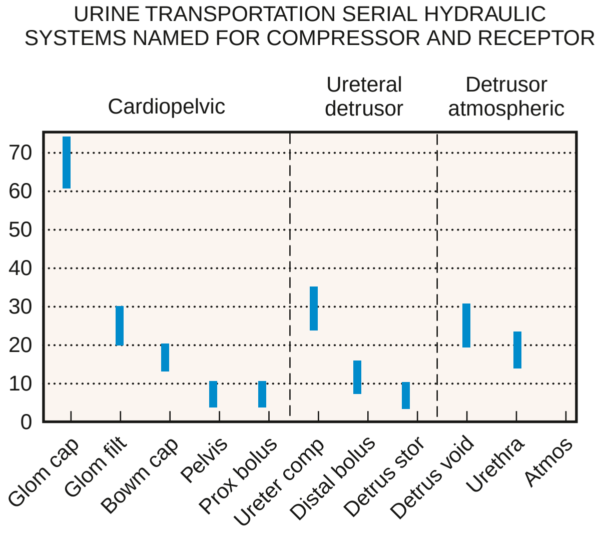


Figure 20-3 Urinary tract physiology versus anatomic site. Atmos, atmospheric; Bowm cap, Bowman capsule; Detrus void, detrusor void; Detrus stor, detrusor storage; Glom cap, glomerular capsule; Glom filt, glomerular filtration; Prox bolus, proximal bolus; Ureter comp, ureter compliance. (From Guyton A. *Textbook of Medical Physiology*. 8th ed. Philadelphia: Saunders; 1991, p 289.)

the fluid and the length of the conduit. Poiseuille's law has many applications in the analyses of our study system, but three require special emphasis. First, the renal circulation is totally unique with two arterioles (afferent and efferent). Minor changes in either arteriole radius amplified by the fourth power dramatically change the arteriole resistance and glomerular filtration pressures; approximately 19% increase in the radius doubles the flow. Also, each nephron is a very long thin conduit when its length is compared with its width. Finally, the hypoplastic proximal adynamic ureteropelvic segment as was discussed earlier is narrower than the normal UPJ and has greater resistance. The UPJ is not just a static conduit, however, and this is not the only factor in its decreased urine transport capability.

LaPlace describes the major determinants and interrelationships of storage of fluid in vesicoelastic containers:

$$P = \frac{T}{\Pi r^2}$$

P is pressure in the container, *T* is the tension or the potential energy of elastic force in the wall of the container, and *r* is the radius of the container. LaPlace's law is applicable in all biologic vesicoelastic containers such as the heart, lung, bladder, and proximal ureter forming the ureteral bolus. An efficient vesicoelastic container is able to accommodate more fluid (matter) and energy (the entering fluid) by elastic stretching of the wall, which allows more liquid to be accommodated, and the energy stored as potential energy of elastic force in the wall, rather than pressure in the contained liquid. If the radius doubles, the tension in the wall (potential energy of elastic force) must quadruple to maintain a constant pressure. An efficient storage system has a high compliance $\Delta V/\Delta P$. In an inefficient system, such as in an inelastic and rigid container, as the radius enlarges, the pressure increases.

LaPlace's law is especially pertinent in two particular situations in the upper urinary tract. The first is the renal pelvis itself: if nephron urine delivery is faster than distal ureteral urine transportation, the efficient pelvis is able to stretch and accommodate the discrepancy of mass (volume of urine) and energy. LaPlace's law also applies to the proximal UPJ hypoplastic adynamic ureteral segment. The inefficient arrangement of muscle, collagen, and ground substances makes the radius and the wall less elastic so that the ureteral bolus volume is restricted.

The law of conservation of mass and energy also applies. In an open system, such as the upper urinary tract, the amount of energy (kinetic and pressure) and mass (urine) put into the system equals the mass and energy in the system plus the amount that has escaped the system. Energy enters in the form of pressure or kinetic energy. It has only three fates: tension in the wall, pressure in the contained urine, or escaping kinetic energy. Similarly, the mass or volume of urine contained in the pelvis has only three fates: it is retained in the pelvis, is delivered down the ureter, or escapes by a pathophysiologic mechanism.

Biohydraulic work and power also are important. Work is force times distance, or in hydraulic terms the volume of liquid transported (pumped) against a given pressure gradient. Biohydraulic power is transport of a given volume of fluid in a given time interval against a given pressure gradient. The kidney dictatorially demands work to be done by the ureter at a given rate specially defined by urine flow rate and bladder pressure. If the UPJ can transport the urine at the required rate (ureteral power delivery), urine does not need to accumulate or escape proximally, and there is a power balance. During increased renal power demands (e.g., diuresis, full bladder) when the ureter is unable to keep up, renal power demand does not equal ureteropelvic power delivery, and a power shortage exists. If such an imbalance exists, law of conservation of mass indicates three possible fates: urine (matter) accumulates, urine escapes or decompresses, or nephron urine output decreases.

The fundamental physiologic problem in congenital UPJ associated with hydronephrosis is that the UPJ has reduced (but not absent) urine transport capability (or power deficiency). This decreased proximal ureteral urine transport efficiency or power deficiency is due to four factors, as follows:

1. The proximal ureter at the UPJ has a decreased radius compared with normal ureters—by Poiseuille's law a higher resistance.
2. The abnormal connective tissue (in amount, distribution, and quality) in the wall, decreased elasticity, and, by LaPlace's law, the volume of the ureteral bolus that can be accommodated are decreased. A cardiac analogy is a heart with decreased stroke volume cannot match the cardiac output of a heart with normal volume at an equal heart rate.
3. From histologic studies showing decreased mural muscle volume and ineffective muscle arrangement, it is reasonable to assume contractility also is decreased.
4. Conduction of peristaltic wave from proximal pacemaker is inefficient.

PHYSIOLOGY OF RENAL HEMODYNAMICS AND GLOMERULAR FILTRATION

The kidneys normally receive about 20% of the entire cardiac output (range 12% to 30%). Only 2% to 3% of total blood flow goes through the vasa recta and medulla. Flow is much more rapid in the cortex and sluggish in the medulla. Pressures in the renal circulation are shown in Figure 20-4. The main points of resistance as indicated earlier are the two arterioles. The pressure is high in the first (glomerular) capillary bed to permit filtration and low in the second capillary bed to permit reabsorption.

The mean pressure in the glomerular bed is 60 mm Hg (82 cm H_2O), and the pressure in the peritubular capillaries is 13 mm Hg (18 cm H_2O). The pressure causing glomerular filtration is equal to glomerular capillary$_{\text{hydrostatic pressure}}$ (60 mm Hg) + Bowman capsule$_{\text{oncotic pressure}}$ (2 mm Hg) − Bowman capsule$_{\text{hydrostatic pressure}}$ (18 mm Hg) − glomerular capillary$_{\text{oncotic pressure}}$ (32 mm Hg) = approximately 12 mm Hg, or 16 cm H_2O. The filtration pressure is increased by increased blood flow because a smaller percentage of fluid is filtered, and an increase in colloid osmotic pressure in the glomerular capillary is not great.

The effects on afferent and efferent arteriolar vasoconstriction are shown in Figure 20-5. From these measurements, one can see that pressures in the renal pelvis must be kept less than 7 mm Hg, or 10 cm H_2O, to maintain renal blood flow and glomerular filtration at optimal levels. From these data, pelvic pressures greater than 12 to 14 mm Hg, or 16 to 20 cm H_2O, would significantly interfere with these two processes (see later discussion on models).

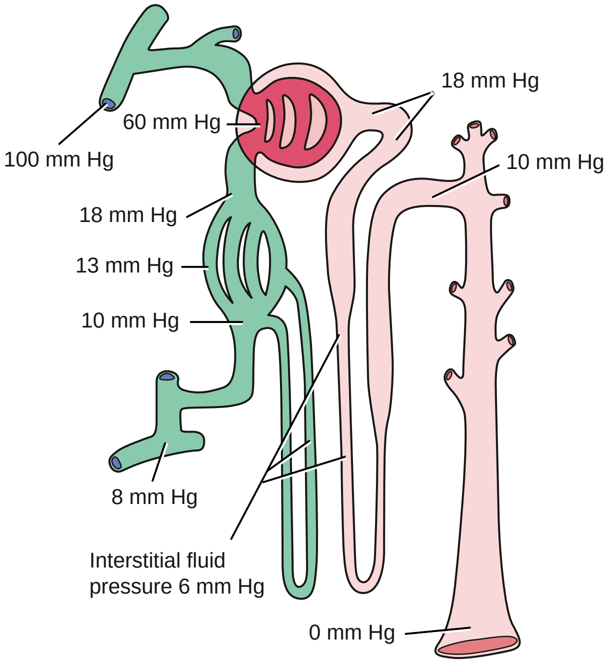


Figure 20-4 Approximate pressures at different points in the vessels and tubules of the functional nephron and in the interstitial fluid. (From Guyton A. *Textbook of Medical Physiology*. 8th ed. Philadelphia: Saunders; 1991, p 289.)

NORMAL PHYSIOLOGY OF CALYCES, INFUNDIBULUM, AND PELVIS

The normal physiology of the calyces, infundibulum, and pelvis was first systematically studied by Kiil.[38] His studies are classic and practical. The applicable principles are the following:

1. The pelvic infundibula are an anatomic confluence to convey the ureter from nephron to ureter.
2. The pelvis is also an important storage container for storing urine and energy if there is a discrepancy between nephron urine delivery and distal ureteral transport.
3. The maximum, mean, and minimum pressures in the pelvis are low (<6.5 mm Hg or <8 cm H_2O), permitting low-pressure egress from the collecting ducts of the nephrons to continue on an almost continuous basis.
4. There is some contractile activity in the pelvis; it is not entirely a passive storage and confluence organ, although these contractile pressures are low.
5. Most important is Kiil's concept of "ureteral cone" to form the proximal ureteral bolus. This is illustrated in his classic original diagram. We have observed and confirmed this concept many times in ureteral fluoroscopy. It consists of passive low-pressure ureteral filling, ureteropelvic closure, ureteral contraction, and further distal course of peristaltic wave.
6. Calyces and infundibular areas are pacemakers for the entire upper urinary tract. Pacemaker cells are cells that develop electrical activity spontaneously. Gosling and Dixon[39-42] provided morphologic evidence that pacemaker tissue resides in the proximal urinary tract in the region of attachment of the minor calyces to the parenchyma.

PROPULSION OF URINARY BOLUS

After extrusion into the ureter, the urine forms a bolus owing to a contraction ring that completely coapts the ureteral wall (Fig. 20-6).[43] The contraction ring at the proximal end of the bolus proceeds along the ureter at a constant velocity. The velocity of the leading edge of the bolus varies so that the width and length of the same bolus vary in different parts of the ureter. Weiss[44] has summarized the ureteral physiology. Contraction waves occur at a frequency of two to six times per minute with the baseline

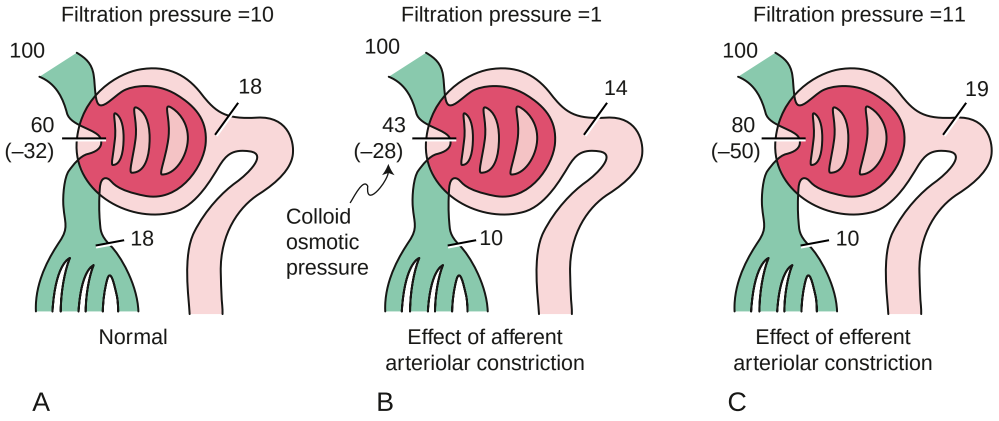


Figure 20-5 Approximate pressures in afferent and efferent arterioles, Bowman capsule, and glomerular filtration during normal circumstances **(A),** afferent arteriolar vasoconstriction **(B),** and efferent arteriolar vasoconstriction **(C).** (From Guyton A. *Textbook of Medical Physiology*. 8th ed. Philadelphia: Saunders; 1991, p 292.)

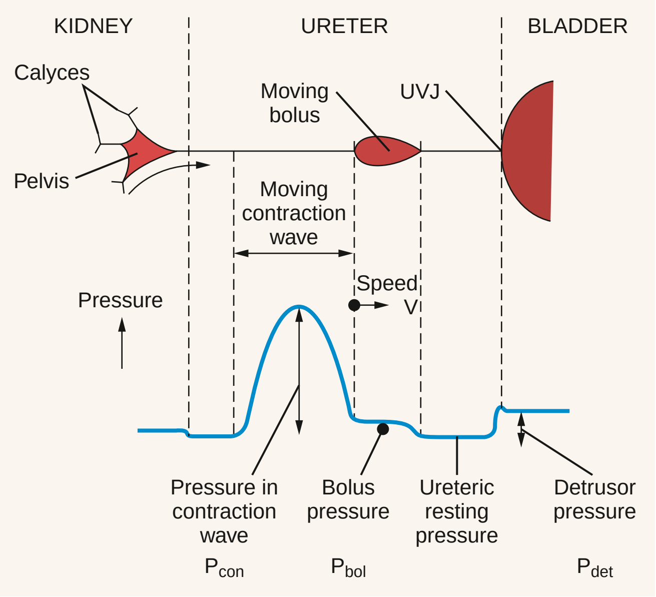


Figure 20-6 Schematic representation of a single bolus in the ureter moving from the renal pelvis to the bladder. UVJ, ureterovesical junction; V, speed of voiding. (From Weiss RM, Coolsaet BL. The ureter. In: Gillenwater JY, Grayhack JT, Howards SS, et al, eds. *Adult and Pediatric Urology*. 2nd ed. St. Louis: Mosby-Year Book; 1987, p 889. Reprinted from Griffiths DJ, Notschaele C. The mechanics of urine transport in the upper urinary tract: the dynamics of the isolated bolus. *Neurol Urodynam*. 1983;2:155. © 1983 Wiley-Liss, Inc. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

pressure of 2 to 6 cm H_2O and contraction pressure of 20 to 60 cm H_2O, and waves are conducted at 2 to 6 cm per second. In establishing this accurate, easy-to-remember guideline, Weiss[44] has quoted the direct measurements of Weinberg.[45-47]

When renal power demand increases with diuresis, normally there is an increase in ureteral bolus volume, increased rate of contraction, and increased contraction pressure, and contraction waves are conducted at increased rate. With increased diuresis and increased bladder, the normal ureter is able to transport a greater volume of urine per unit time into a bladder with higher pressures. Ureteral power delivery is increased. As mentioned earlier, this response mechanism is interfered with in proximal hypoplastic adynamic ureteral segment. Weiss and Biancani[48] also provided practical evidence that ureteral bladder pressure gradients and ureteral workloads increase as the bladder fills (Fig. 20-7).

PHYSIOLOGIC ANIMAL MODELS EMPLOYED AND LESSONS LEARNED

Complete Ureteral Obstruction

The classic basic studies of Hinman were mentioned previously in the section on Fundamental Pathophysiology. If you are reading this chapter out of sequence, please review his invaluable contributions. These contributions have been added to and updated by other researchers.[49-52] This research documents a triphasic response in ureteral pressure and renal blood flow after unilateral ureteral ligation (Fig. 20-8). This research also confirms by completely different methods the progressive and eventually irreversible decrease in renal blood flow (Fig. 20-9) in chronic complete obstruction.

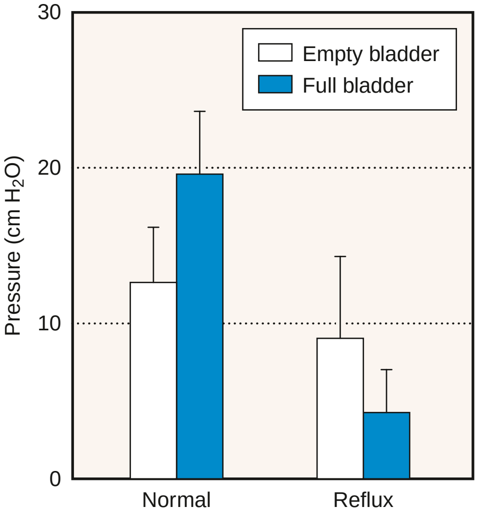


Figure 20-7 Pressure gradient across the ureterovesical junction. (From Weiss RM, Coolsaet BL. The ureter. In: Gillenwater JY, Grayhack JT, Howards SS, et al, eds. *Adult and Pediatric Urology*. 2nd ed. St. Louis: Mosby-Year Book; 1987, p 891.)

Pressurized Nonobstructive Hydronephrosis Model

Fung at the Hospital for Sick Children in Toronto has used an anesthetized pig model in which both ureters are cannulated and the experimental kidney drains to an open reservoir with pressures of 9 cm H_2O, 10 cm H_2O, 20 cm H_2O, 30 cm H_2O, and 40 cm H_2O above the renal pelvis. The contralateral kidney drains to a similar reservoir kept at the same level of renal pelvic pressure. An imposed experimental pelvic pressure of 10 cm H_2O has minimal effect on renal blood flow and renal oxygen consumption, but pressures of 20 cm H_2O, 30 cm H_2O, and 40 cm H_2O progressively decrease renal blood flow (Fig. 20-10). Similarly imposed experimental pelvic pressures of 0 cm H_2O, 10 cm H_2O, and 20 cm H_2O have little or no effect on apoptosis (programmed cell death) in various parts of the ureter. Pressures of 30 to 40 cm H_2O dramatically increase the apoptosis ratio (by a fraction of 30-fold to 40-fold) at all levels of the nephron (Fig. 20-11). Constant imposition of renal pelvic pressure (nonobstructive pressures of 40 cm H_2O) for 24-hour periods shows that this dramatic increase in apoptosis begins as early as 4 hours.

These studies have correlated well with Fung and colleagues'[53] direct measurements of renal pelvic pressure, and renal blood flow in patients as measured by renal Doppler and resistive index studies. Progression in renal pelvic pressures from 20 to 40 cm H_2O progressively decreases renal blood flow in pediatric patients.

Micropuncture Data

All the quoted figures in this section on physiology of renal hemodynamics and glomerular filtration have basically been gleaned from micropuncture data in various mammals. These data correlate well with experimental hydronephrosis data and direct patient measurements of Fung, Kiil, and others.[38,53] Normal pressures driving fluid from Bowman capsule down the nephron are only about 10 to 20 mm Hg (13.6 to 26 cm H_2O), depending on the animal used. Pressure at the distal nephron and at the ureter in the pelvis is usually constantly 6.5 mm Hg

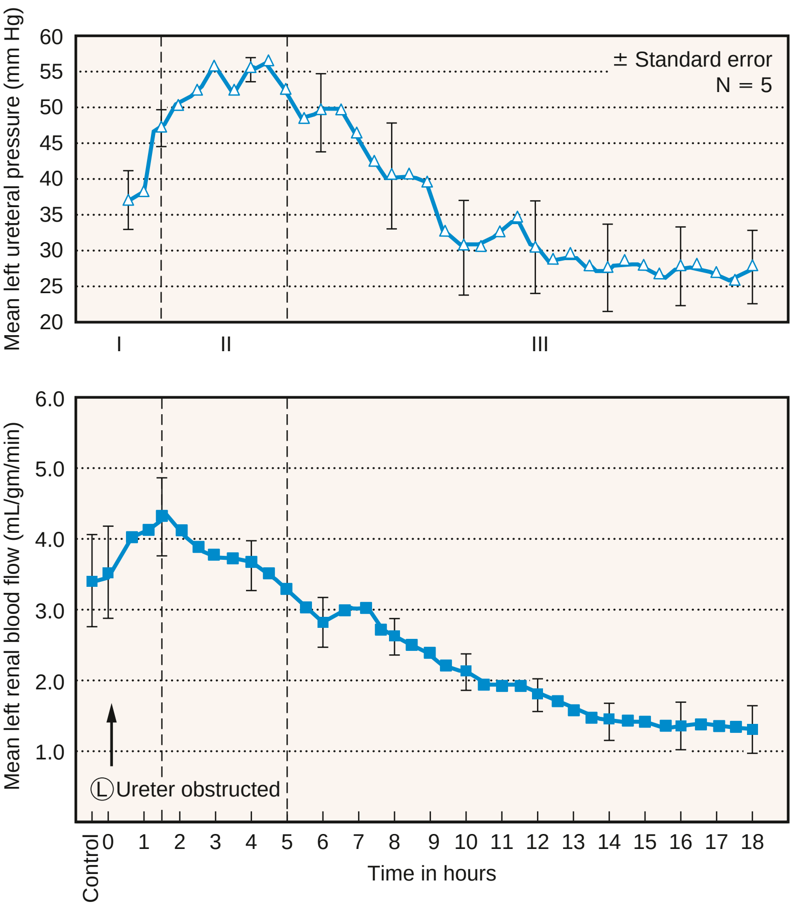


Figure 20-8 Triphasic relationship between ipsilateral renal blood flow and ureteral pressures after complete ureteral occlusion. (From Gillenwater J. Hydronephrosis. In: Gillenwater JY, Grayhack JT, Howards SS, et al, eds. *Adult and Pediatric Urology*. 2nd ed. St. Louis: Mosby-Year Book; 1987, p 793.)

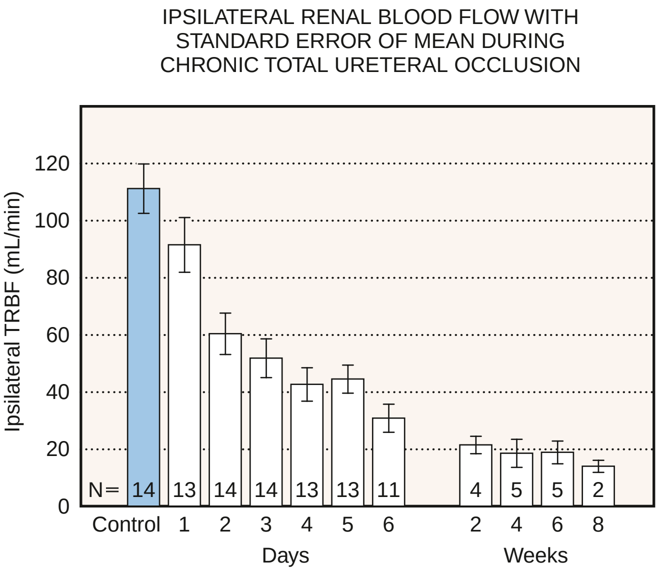


Figure 20-9 Changes in left renal blood flow with chronic total left ureteral occlusion. TRBF, total renal blood flow. (From Gillenwater J. Hydronephrosis. In: Gillenwater JY, Grayhack JT, Howards SS, et al, eds. *Adult and Pediatric Urology*. 2nd ed. St. Louis: Mosby-Year Book; 1987, p 795.)

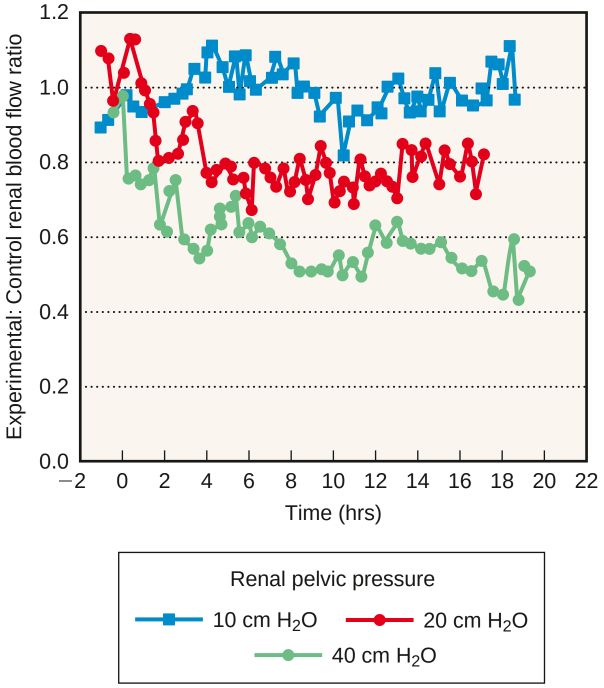


Figure 20-10 Changes in renal blood flow with increased imposed pelvic pressures without obstruction.

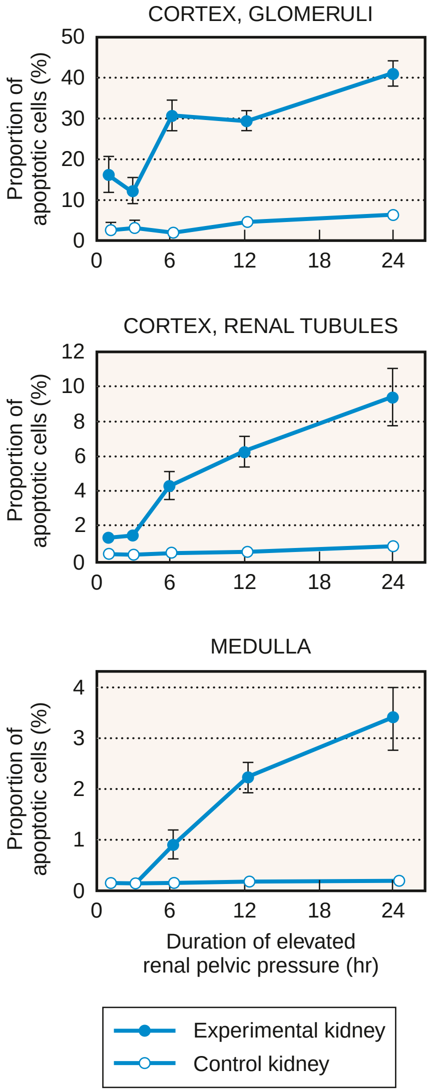


Figure 20-11 Changes in the apoptosis rate in various parts of the nephron with imposed increased intrapelvic pressures without obstruction over 24 hours. Constant renal pelvic pressure (40 cm H_2O), variable duration.

(8 cm H_2O); the renal pressure gradient between the proximal and distal nephron is small. Renal pelvic pressures of 11 to 14 mm Hg (13 to 20 cm H_2O) begin to interfere with glomerular filtration and renal blood flow. Pelvic pressure of 30 to 40 cm H_2O sustained for 4 hours begins to inflict renal damage by ischemia and increased rate of nephron cell apoptosis.

Long-term Models of Hydronephrosis Caused by Inefficient Ureteral Transport

The most reliable model to cause hydronephrosis is to bury the ureter of the experimental kidney in the ipsilateral psoas sheath so that urine transport continues, but efficiency is impaired. This model has been used by Homayoon and colleagues[54] in rabbits and Feng (private communications) in swines. These authors have again shown the longer the experiment, the more severe the loss of renal function. Feng's experiments have confirmed that renal ischemic atrophy occurs. These experiments also have cast down the reliability of split nuclear renal function studies versus split inulin clearance.

Renal Excision Model

Renal excision models involve measurement of serum creatinine, GFR (usually inulin), and renal reserve. Following this, there is a total removal of one kidney and removal of a known percentage (based on water volume displacement) of the contralateral kidney with subsequent measurements of serum creatinine, GFR, and renal reserve. These studies show it is possible to remove greater than 75% to 80% of the nephrons and not to affect measurable GFR or serum creatinine. Renal reserve (ability to increase GFR with amino acid load) is impaired. The message of this model is that GFR measurements alone are not good prognostic indicators of mild or moderate irreversible significant nephron loss.

Complete Ureteral Obstruction in Utero

Peters and coworkers[55,56] obstructed ureters and urethras in fetal sheep at 55 to 60 days of gestation. Three distinct patterns of renal pathology were shown: hydronephrotic, cystic with moderate hydronephrosis, and dysgenesis. These kidneys showed dramatically different responses to the same in utero ureteral and urethral occlusion. Some were completely destroyed (rendered "hopeless"), whereas others had severe hydronephrosis or moderate hydronephrosis with cysts. These "hopeful" kidneys all had histologically intact nephrons and in a clinical situation were capable of contributing meaningful renal function. The main difference between the hopeful and hopeless kidneys was the incidence of spontaneous decompression, which occurred in none of the hopeless dysgenic kidneys (0 of 8), in all of the cystic moderate hydronephrotic kidneys (5 of 5), and in most of the hydronephrotic kidneys (14 of 26).

Ischemic Injury Model

Jones and colleagues (private communications) attempted to delineate the molecular mechanisms of injury resulting from unilateral renal obstruction. In rat models with unilateral obstruction, they were able to show an upregulation of inflammatory chemokines such as MCP-1, Fas, and Fas ligand from the obstructed kidney only. These ischemic injury response elements were attenuated with bioflavonoids.

Partial Obstruction (Inefficient Ureteral Urine Transport) in the Developing Kidney

The model of partial obstruction (inefficient ureteral urine transport) in the developing kidney most closely mimics the clinical situation. The most common model method reported was to bury one ureter in the psoas muscle in newborn rats[57] or guinea pigs.[58] This resulted in significant dilation of the pelvis, decrease in significant GFR (17% to 44%), decrease in number of glomeruli, decrease in renal blood flow, and decrease in ipsilateral renal growth. There was also contralateral renal hypertrophy. The greater the duration of transport inefficiency, the greater the damage was also shown in these studies. Early release resulted in reduced severity of parenchymal injury.[57] Experiments by Chevalier[59,60] and Taki[58] and their colleagues with this type of model showed greater damage in neonatal than adult kidney and less recovery with release.

The study by Provoost and coworkers[61] of congenitally hydronephrotic Wistar rats showed in adolescent animals that the affected kidney contributed only 25% of the total GFR. With two kidneys, the animals did not progress to irreversible renal failure. Such congenital lesions reduced ureteral transport efficiency in a solitary kidney, however, and quickly progressed to end-stage renal failure, indicating renal reserve impairment.

Molecular Biology of Renal Injury in Hydronephrosis

The studies of Gobe and Axelsen[62] indicate that increased rate of apoptosis has a controlling role in renal atrophy associated with significant hydronephrosis. Gobe and colleagues[63] showed apoptosis primarily in the distal tubule epithelial cells. The methods of imposing hydronephrosis were different. *Apoptosis* is a term given to a distinct form of cell death in which the cell dies as a result of a seemingly programmed event. An inherently controlled cell death implies a complex form of multiple interacting variables including triggers and inhibitors. Studies by Walton and associates[64] indicate expression of epidermal growth factors significantly declines in the 72 hours after obstruction. In contrast, the expression of transforming growth factor increased in the obstructed kidney.

CHANGES IN RENAL AND UPPER URINARY TRACT FUNCTION IN FETAL, NEONATAL, AND EARLY CHILDHOOD

There are significant changes in the kidney and upper urinary tract before and after birth as a result of development, growth, and maturation. These changes must be considered in interpretation of clinical tests, selection of therapy, and evaluation of results. Campbell and colleagues[65] showed that the fetus late in gestation can produce four to six times the urine volume per kilogram as a newborn. Similarly, a newborn existing almost entirely on a liquid diet can concentrate urine to only about 600 mOsm, whereas later in childhood concentrations of 1200 mOsm are routinely achieved. A late term fetus produces relatively more urine (per kilogram) than a newborn, who produces relatively more urine (per kilogram) than a child. We have earlier stated that hypoplastic adynamic ureteral segments represent a relative ureteral urine transport inefficiency, or what we like to term a "power shortage." We have also shown earlier that severe diuresis can overwhelm and cause severe dilation in an otherwise normal system. The studies of Zedric and collegaues[66] and Weiss[44] showed that the upper and lower urinary tract in very young children is more elastic, more compliant, and more distensible than the urinary tract in adults. Pragmatically, we think all of the developments are interrelated and explain many of our clinical findings.

The third-trimester fetus and the newborn produce larger volumes of urine per kilogram. This is a temporary phenomenon, and the more distensible urinary tract allows for mild dilation, while maintaining normal renal pelvic pressure and renal blood flow. As urine output declines, the power demands imposed by the kidney on the ureter decrease, and the mildly inefficient proximal ureter may now be able to meet reduced power demands of the kidney, and this ureteropelvic power shortage no longer exists. We believe this is the explanation for "transitional hydronephrosis" of newborns and infants described by Homsy and coworkers.[67]

In addition to change in renal tubules and pelvic compliance, glomerular filtration per square meter significantly increases until age 1 to 3 years. During this interval, the GFR per 1.73 m^2 practically doubles over and above changes with growth. This is very important in evaluating series of outcomes of GFR increase whether it was achieved by watchful waiting or surgery. One must differentiate between GFR improvement because of spontaneous resolution of the problem, GFR improvement because of skillful well-timed surgery, and GFR improvement because of maturation and growth.

ETIOLOGY AND PATHOLOGY OF CONGENITAL URETEROPELVIC URINE TRANSPORT INEFFICIENCY

Most authors over the years have classified the pathologic lesions at the UPJ into *intrinsic* and *extrinsic* abnormalities. This separation remains useful in understanding and treating the clinical problems.

Intrinsic Pathology

These basic histologic types have been described over the years by many authors. Cussen[68,69] systematically outlined the anatomic function of these lesions. He first stressed that physical patency exists in all of these cases. The lumen is narrow, however. The lining is normal, but is surrounded by a reduced number of leiomyocytes (small muscle cells). The individual smooth muscle cells are of normal size.[70] Starr and colleagues[71] also studied these lesions histologically and observed additional findings, including increased collagen between the muscle bundles, increased elastin in the adventitia, and rearrangement of the orientation of muscle fibers.

Many authors noted predominance of longitudinal muscles, excessive collagen in and around muscle cells, and attenuated muscle bundles. Hanna and colleagues, Notely, and others[72-75] learned from electron microscopic studies of pathologic UPJs that there is excessive collagen fibers and ground substance between and around the muscle cells. As a result, muscle cells are widely separated, and their points of connection or nexus are attenuated. Gosling and Dixon[76] also noted electron microscopic histologic abnormalities at the UPJ.

In hundreds of cases over the years, we have almost always grossly observed the following practical points:

1. The described intrinsic lesions occur in almost 100% of cases.
2. The lumen is small but physically patent.
3. The mural wall is thin.
4. The elasticity of the wall tested by placing both pincers of a nontoothed Iris forceps in the lumen is significantly reduced compared with the distal normal ureter in the same patient.

Our final conclusion is that there is an interference with peristalsis propagation across the UPJ and interference with urine bolus formation in the proximal ureter. This is best labeled as a "hypoplastic adynamic ureteral segment" at the UPJ. As we show later, this segment of conduit actively transports urine, albeit at low workloads (i.e., low urine volumes into lower bladder pressures), but cannot efficiently adjust to increased workloads (high urine volumes or higher bladder pressures) in an effective manner.

Other authors have described, beginning with Ferjon[77] in 1894, "flap valve" as an etiologic cause at the UPJ. More recently, Maizels and Stephens observed similar lesions.[78] We have occasionally observed the benign mesodermal polyp as described by Gup.[79]

Extrinsic Pathology

Extrinsic pathology refers primarily to the aberrant crossing vessels, fibrous band adhesions, kinks, and anomalous takeoffs. Mayo[80] probably offered the first lively description of the hazard of unexpected blood vessels crossing the UPJ. Stephens[81] coined the term *ureterovascular tangle* to describe the condition wherein the proximal ureter is angulated, distorted, and compressed by vessels that supply the lower pole of the kidney. There seems to be little doubt that such vessels occur in about 25% of clinically significant ureteropelvic urine transport inefficiencies.[82]

There also seems to be little debate about the embryology of these vessels. During fetal development, the maturing kidney ascends in the retroperitoneum. The kidney also rotates as the pelvis goes from an anterior to medial position. During this ascent and rotation, the kidney has segmented vessels from the aorta arranged in a ladder pattern. As the kidney ascends, it derives its blood supply from higher vessels and sheds lower ones.

Rearrangement also occurs so that the pelvis usually comes to lie posterior to the vessels—vein-artery-pelvis, anterior to posterior. It is conceivable that abnormal spatial and temporal progression of renal ascent and rotation combined with renovascular formation may lead to unfavorable ureterovascular configurations. There is also little doubt that such vessels can trap the UPJ and in association with inefficient drainage caused primarily by an intrinsic lesion can significantly angulate, kink, aggravate, and exaggerate the severity of the hydronephrosis.

There is also little controversy that such vessels must be accurately diagnosed either preoperatively or intraoperatively, and these individual anomalies must be dealt with by a successful strategy. Failure to diagnose and treat successfully can lead to highly undesirable hemorrhage and because they are end-arteries, renal ischemia.

The present debate concerning crossing or anomalous vessels is whether they can primarily cause significant ureteropelvic transport inefficiency in the absence of significant intrinsic lesion. Several noted authors[83,84] dogmatically indicate that these lesions occasionally may cause such problems, but offer little objective data to substantiate their opinion. Our own experience is that anomalous vessels are associated with secondary problems in 20% of cases, but rarely if ever cause significant ureteropelvic transport inefficiency in the absence of intrinsic problems.

With the introduction of endopyelotomy, which involves indirect and occasionally accidental exposure of immediately adjacent vessels, there has been a major resurgence of articles dealing with basic anatomy and imaging of these crossing vessels. In a published symposium on hydronephrosis, 15% of the articles dealt with these subjects. The summarized findings indicate that in 65% of surgically managed UPJ lesions there was a prominent artery or vein on the anterior surface of the pelvis within 1.5 cm of the UPJ. In 6.8% of the cases, there was an inferior polar artery, crossing anterior to the UPJ. In 27% of cases, there were vessels crossing posteriorly within 1.5 cm of the UPJ.[85] The take-home message is that any endopyelotomies done without direct visualization of the vessels should be done on the lateral aspect where significant vessels seldom occur. An important caveat to that principle is a malrotated or otherwise anomalous kidney.[86]

Preoperative or intraoperative imaging of such vessels can be accomplished by conventional angiography,[87] intra-arterial digital subtraction angiography,[88] endoluminal ultrasound,[89] and spiral CT.[90] Conventional angiography is invasive and expensive, but also accurate. Digital subtraction angiography is not accurate enough. The latter two modalities seem to be current methods of choice.[86]

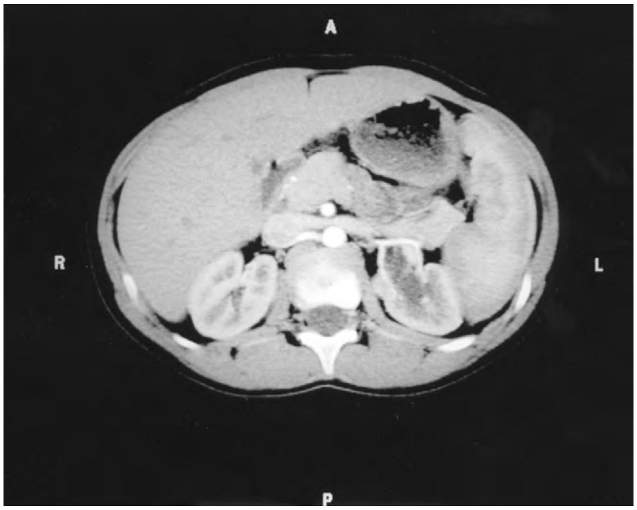


Figure 20-12 CT scan of the left kidney with two aberrant renal vessels entrapping the ureteropelvic junction, creating hydronephrosis.

The debate of whether crossing vessels are a primary, secondary, or associated etiologic factors recurs every second decade ("déjà vu all over again"—Yogi Berra). Sectioning of vessels as the primary operative therapy was tried in the 1950s and 1960s.[91-93] Similar operations for displacing vessels were performed in the 1970s. This disregarded technique was performed again in the 1990s using laparoscopy.[94] We are opposed to the procedure for three reasons:

1. These are all end-arteries, and renal ischemia occurs in 100% of cases.
2. The end-arteries occasionally can supply 30% of the kidney's blood supply.[95]
3. There are no long-term data to suggest that it works.

Reports by Van Cangh and associates[96] suggest that endopyelotomy may not only be more dangerous with associated aberrant vessels, but also may be less successful (82% to 33%) in moderate hydronephrosis. It is not surprising that anomalous vessels are seldom (if ever) the primary etiology, but they frequently are important secondary contributing etiologic factors. Figure 20-12 shows a case treated with two previous open pyeloplasties at outside hospitals. Severe intermittent symptoms continued. Imaging studies (spiral CT) showed failure to transpose successfully UPJ from entrapping vessels. The third open dismembered pyeloplasty and displacement was successful. Endopyelotomy fails to displace the UPJ in cases in which aberrant vessels are a significant etiologic factor. Impaired drainage may persist even if the primary intrinsic factor has been improved.

Bands, Kinks, and Anomalous Insertions

There is little or no controversy that bands and kinks are commonly associated problems, and that they can frequently aggravate the severity of the hydronephrosis. Park and Bloom[37] suggested that such bands are more common in older children with symptomatic ureteropelvic urine transport problems. We agree with Flashner and King[84] that when they frequently occur in the absence of prior infection, it tends to be a significant clinical problem. Nephropexy was previously a common operation. Now it is seldom performed. Only one scientific piece of information gives any evidence to the importance of mobility. Ellis and colleagues[97] showed pressure flow studies can be altered by positional variation. Personally, for several decades we have not performed a nephropexy on a fixed kidney with pyeloplasty. In contrast, Park and Bloom[37] noted in several reoperative cases that certain postures caused "kinking, angulation, and obstruction," although the previously repaired UPJ site was widely patent.

Vesicoureteral Reflux—Causation versus Association

We acquire a VCUG in all patients with hydronephrosis. Data presented earlier in the chapter showed that lower tract dysfunction, reflux, or other abnormalities of the ureterovesical junction can be the primary etiology of the upper tract dilation and warrant early specific diagnosis. Reddy and Mandell[36] reported an incidence of VUR in 14% of patients with limited detection of upper tract dilation by ultrasound. Conversely, Park and Bloom[37] reported significant UPJ problems in only 0.5% of cases with VUR. This association of synchronous UPJ problems with VUR is five times as great in severe reflux (grades IV and V) than in mild reflux (grades I through III).

Ureteropelvic Junction Problems and Renal Calculi

Inefficient urine transport across the UPJ and renal calculi frequently coexist. Rickwood and Reiner[98] found 1.2% of pediatric patients diagnosed with prenatal hydronephrosis in the absence of reflux had renal calculi. Snyder and coworkers,[99] reviewing the Boston's Children Hospital series in 1980, noted that 3% of patients with UPJ problems had calculi. This incidence is higher in adults, reportedly 11% to 20%.

The cause of stones in this situation is mixed. Stasis and infection undoubtedly play an important role, particularly when calculi have a struvite composition; this is supported by the fact that stone recurrence after pyeloplasty and removal is low.[100] Husmann and colleagues[101,102] showed, however, that 71% of cases of nonstruvite stones and coexisting UPJ problems had metabolic abnormalities. This hypothesis is supported by the fact that 43% of recurrent calculi in this patient cohort occur in the contralateral kidney. An important controversy exists whether the stone is secondary to the UPJ problem or vice versa. Evidence in children indicates that the UPJ problem is primary. In adults, cases are reported where stone removal before has resolved the UPJ problem. In any case, there is little doubt that stone at the UPJ may worsen the degree of stasis, and increase the likelihood of secondary infection and renal damage.

Ureteropelvic Junction Problems in Anomalous Kidneys

Ureteropelvic urine transport problems can occur in otherwise normal kidneys, but also occur in anomalous kidneys, including horseshoe or fused kidney, duplex kidney, and ectopic kidney.

Horseshoe Kidney

Horseshoe kidney occurs in about 1 per 500 live births. Approximately 15% of these cases have an associated ureteropelvic urine transport efficiency problem. This is at least 15 to 20 times the association rate in a normal kidney; there seems to be an intrinsic tendency for ureteropelvic urine transport problems to occur in horseshoe kidney. At times in the past, the isthmus itself was thought to be a secondary extrinsic factor, and simultaneous symphysiotomy was performed. The consensus now is that division of the parenchyma is almost never necessary. The diagnosis is still important to make preoperatively because it affects the incision and approach if open pyeloplasty is performed, and the individual vascular configuration affects the technical details of repair. We personally still prefer an open technique using an extraperitoneal approach, and position at 45 degrees for unilateral lesions and reserve the transperitoneal approach for simultaneous bilateral pyeloplasties. Retrograde and antegrade endopyelotomies have been used successfully, however. In this situation, care has to be taken with the anomalous vessels (see later discussion).

Duplication of Renal Collecting System

Duplication of the collecting system occurs in 0.5% of unselected populations. In contrast to patients with horseshoe kidney, patients with duplex kidney do not seem to be at much increased risk for associated ureteropelvic urine transport inefficiency problems. Snyder and coworkers[99] reported 4 cases of duplication in a series of 195 cases with UPJ problems. In most cases, UPJ problems have been restricted to the lower pole. Typically, the upper pole ureter tends to have a single infundibulum without a true pelvis. It also has been suggested that the significant predilection for involvement of the lower pole can be related to the high incidence of significant VUR into the lower pole of a complete duplicated system.

The associated UPJ problem may occur with an incomplete duplication, complete with ectopic ureter, or even occasionally complete with ectopic ureterocele. Similar to horseshoe kidney, a preoperative imaging protocol that successfully shows the exact individual anatomy and physiology of a particular case should be employed. This imaging is important so that associated problems can be dealt with simultaneously and to improve anatomic accuracy. In most cases of UPJ with duplex kidney, the only intraoperative modification is to confirm the correct ureter. Standard dismembered pyeloplasty can be performed in most cases (see subsequent section). Associated duplex problems present interesting challenges that can be surgically corrected simultaneously if a specific accurate diagnosis is obtained preoperatively, a careful individual operative strategy is chosen, and informed consent is obtained. Previous technical failure in pyeloplasties in duplex kidney may allow imaginative individual solutions.[103] Also, percutaneous endopyeloplasty, retrograde pyelotomy, and laparoscopic solutions all have been reported.

As mentioned earlier, UPJ problems resulting from hypoplastic adynamic segments virtually never occur in the upper pole. We agree with Koyanagi and associates[104] that when there is an upper pole obstruction, it is more analogous to a Fraley syndrome with crossing constricting vessels. This condition is managed by dividing the upper pole ureter, transposing it to the other side of the vessels, and performing reanastomosis.

Ectopic Kidney

Renal ectopy refers to a kidney outside the renal fossa. It is a rare finding, occurring in 0.01% to 0.08% of patients.[105] According to Gleason and coworkers,[106] sites include pelvic (55%), crossed (32%), lumbar (12%), and thoracic (1%). Approximately half of such kidneys are hydronephrotic. Hydronephrosis is due to various causes, including UPJ problems (37%), VUR and lower tract problems (26%), and hypoplastic adynamic segments at the ureterovesical junction (15%). All cases require lower tract imaging and accurate anatomic (not just functional) upper tract imaging. We currently prefer CT urograms with simultaneous ureteral fluoroscopy. Surgical correction requires special consideration.[107-109] Position, incision, and approach must be individualized; in most cases, a modified Gibson incision allows an extraperitoneal approach. Open pyeloplasty is usually successful. Experience with less invasive techniques is limited.[100]

CLINICAL PRESENTATION

The clinical presentation changed dramatically after the advent of widespread maternal ultrasound screening in approximately 1978. Before prenatal ultrasound, children primarily presented with symptoms. Presentations include febrile urinary tract infections, abdominal masses, pyuria, pain, hematuria, and gastrointestinal symptoms. The hematuria may follow trivial or mild abdominal trauma. Fifty percent of all palpable abdominal masses are renal, and almost 50% of those are hydronephrosis. Other, less common presentations include failure to thrive, anemia, sudden onset of hypertension, and urinary extravasation.

UPJ problems are often associated with other congenital anomalies, including imperforate anus, contralateral multicystic kidney, congenital heart disease, VATER syndrome, (*V*ertebral, *A*nus, *T*rachea, *E*sophagus, *R*enal), and esophageal atresia. In patients with the established diagnosis, a renal ultrasound examination should be performed. Now most cases are asymptomatic and are diagnosed on routine maternal ultrasound screening.

DIAGNOSTIC TESTS

In ordering diagnostic tests, the clinician should ask the following questions:

1. What information do I seek, or what question do I wish to answer?
2. What is the most accurate test for answering this question?
3. What is the most effective method of answering the question?
4. Can I answer more than one question simultaneously with a single test?
5. Is the question really relevant to the patient—will it add to the selection, safety, and success of the management strategy?

The last 2 decades have given rise to a wide variety of imaging and other diagnostic procedures. The options are numerous and confusing. Most authors review diagnostic tests by methodology. This is a standard approach, but we prefer to make the technology work for us and for the patient. We prefer to start with the question we wish to answer:

1. Is there abnormal fluid collection in the fetal kidney?
2. Are the prenatal findings reconfirmed after birth?
3. Are the abnormal findings in the lower urinary tract the primary cause of the hydro(uretero)nephrosis?
4. Is the urinary tract infected?
5. Is there associated VUR; if so, how severe?
6. What is the anatomic and functional status of the contralateral kidney and upper urinary tract?
7. Are there calculi proximal to the UPJ; if so, how many, and what is the possible etiology?
8. Has pyelonephritis scarring damaged the affected kidney?
9. Has the affected kidney been damaged by ischemia and atrophy; if so, how severe?
10. Does UPJ lesion occur in the kidney with anomalous ascent?
11. What is the differential function of the affected and contralateral kidney; is the function stable, improving, or deteriorating?
12. How severe is the dilation of hydronephrosis—in absolute and relative terms?
13. What is the anatomy of the calyces?
14. What is the anatomy of the anomalous vessel immediately adjacent to the UPJ?
15. What is the efficiency of urine transport across the UPJ—improving or deteriorating?
16. Is there evidence of renal ischemia?
17. What is the total renal function?
18. Is there a normal spine?

Indications for Maternal-Fetal Ultrasonography

The use of maternal ultrasound is influenced by geographic, economic, and cultural idiosyncrasies. In most developed countries, most pregnant women are examined with this technique. The standard general indications are presence of pregnancy and patient consent. Specifically, more imperative indications include discrepancies in expected fundal height for gestational age, suspected oligohydramnios or polyhydramnios, elevated levels of maternal serum alpha-fetoprotein (associated with neural tube and genitourinary defects), and a history of previous pregnancies associated with congenital anomalies.

Maternal Antenatal Ultrasonography

Maternal antenatal ultrasound is one area in which there is no medical controversy. The selection is unanimous because of safety and sensitivity. The technique involves no damaging radiation, is noninvasive, has no side effects, is not expensive, and is often an enjoyable experience for the mother. It gives valuable information, including the status of the contralateral kidney; amniotic fluid volume; position of the placenta; maturity of the child; status of head, spine, heart, lungs, and limbs; sex of the child; bladder distention and emptying capability; whether the lesion is unilateral, bilateral, or solitary; and sometimes differentiation of hydronephrosis from hydroureteronephrosis. Timing of protocols varies, but important landmarks indicated in embryology bear repeating, as follows:

14th week—kidneys can occasionally be visualized
16th to 18th week—kidney is routinely visualized; nearly all the amniotic fluid is urine
20th week—renal medulla, pyramids, and sinus fat are routinely visualized
24th week—some lesions are not detectable before then
28th week—most sensitive time for fetal urinary tract evaluation; bladder is visualized

For all these reasons, we personally recommend a study at 20 weeks and a second study at 28 weeks of gestation. Subsequent studies depend on individual circumstances. If urinary tract dilation is detected, the following questions need to be answered with further, same-setting evaluation:

1. Does dilation involve one or both kidneys or a solitary kidney?
2. How severe is dilation and echogenicity of kidney?
3. Is it hydronephrosis or hydroureteronephrosis?
4. What is the bladder volume and bladder emptying time?
5. What is the sex of the child?
6. What is the amniotic fluid volume?

It is very important to detect oligohydramnios, particularly in severe bilateral or solitary kidney problems. Criteria for oligohydramnios (<500 mL) include measurement of a single deepest pocket of less then 5 cm diameter and two amniotic fluid pockets of less than 15 mm diameter.[2]

Table 20-1 Society of Fetal Urology Grading System

Grade	Renal Pelvis	Calyces	Parenchyma
0	N	N	N
I	Slight dilation	N	N
II	Moderate dilation	Mild caliectasis	N
III	Large dilation	Moderate caliectasis	N
IV	Severe dilation	Severe dilation	Thinning

N, normal.

The severity and significance of dilation are enhanced by application of the Society of Fetal Urology (SFU) grading system (Table 20-1). Semiquantitative judgment of severity also can be obtained by measurement of the anteroposterior diameter of the renal pelvis in the transverse plane and the diameter of the kidney. Increased anteroposterior diameter of the renal pelvis of 3 to 10 mm occurs in 18% of fetuses after 24 weeks (i.e., second ultrasound). A pelvic diameter of greater than 10 mm at an anteroposterior pelvis-to-anteroposterior kidney ratio of greater than 0.3 correlates with functional significance according to Reddy and Mandell.[36,110] Further ultrasound scans are indicated in the following situations:

1. Bilateral or solitary kidney problems
2. Progression of severity
3. Oligohydramnios
4. Renal architecture (corticomedullary junction) absence, which suggests bilateral hydronephrosis dysplasia of kidneys.

Amniocentesis and Assessment of Fetal Urine Function

Amniocentesis is an invasive procedure to be done only by experienced personnel in patients whose renal ultrasound scans have shown severe problems (see earlier). The goal here is to identify fetuses that are at risk while in utero of total renal destruction and pulmonary hypoplasia when there is a reasonable hope of beneficial treatment. This investigation is not indicated in most cases. It is applicable only to cases of grade IV (SFU) bilateral kidneys or solitary kidney (or strong suspicion of renal dysplasia) with oligohydramnios and determination by serial studies. These tests currently consist of two types: amniotic fluid (fetal urine) to assess fetal tubular function and evaluation of proteins in fetal serum (obtained by fetal amniocentesis) to assess fetal GFR.

Between 16 and 21 weeks of gestation, the fetal urine normally becomes progressively more hypotonic because of selective tubular reabsorption of sodium and chloride in excess of free water. The most quoted values for fetal urinary (amniotic fluid), electrolyte, and osmolality abnormalities indicative of "impaired" renal function in the fetus with detectable upper urinary tract dilation are as follows:

1. Osmolality less than 210 mOsm/L
2. Urinary sodium less than 100 mEq/L
3. Urinary chloride less than 90 mEq/L
4. Urinary output less than 2 mL/hr

Urinary calcium level (normal <8 mg/dL) is the most sensitive indication of renal dysplasia (100%), but it has a demonstrated specificity of only 60%. Elevation of β_2-microglobulin in fetal serum or urine (>4 mg/L) is pathologic in fetuses who have an elevated creatinine 1 year postnatally. This protein and α_1-microglobulin are elevated in renal dysplasia.

Postnatal Ultrasonography

There is very little debate about the type of examination, but there is about the timing of the test and necessity for re-examination. Transitory neonatal dehydration lasts approximately 48 hours.[84] For minor problems in mild and moderate cases, imaging should be done after 48 hours. In severe cases (bilateral, solitary, oligohydramnios, or very large), we recommend doing the examination earlier.

Although renal ultrasound is an ideal noninvasive method to detect infant hydronephrosis, the significance of the upper tract dilation is more difficult to assess because it does not reveal renal function.[26,111] Ultrasound is often operator dependent, and the designation of the grade of hydronephrosis is often subjective. Ultrasound cannot adequately assess the renal parenchymal damage resulting from the underlying disease process. In a study of 255 renal units with reflux, the postnatal sonogram was normal in 177 (70%) of the examined cases.[112]

Postnatal Voiding Cystourethrogram and Nuclear Cystogram

VUR, anterior or posterior urethral valves, ectopic ureteroceles, Hutch diverticulum, and neurogenic bladder may be primary or important associated factors in the detected hydronephrosis. Early accurate diagnosis is important in successful safe management. We strongly prefer conventional VCUG versus nuclear cystogram.

1. Both modalities involve catheterization (i.e., no advantage).
2. Conventional VCUG can diagnose other ureterovesical junction problems, such as Hutch diverticulum and ectopic ureterocele—a significant advantage of VCUG.
3. VCUG can diagnose posterior urethral valves.
4. VCUG gives other details in bladder anatomy (shape, wall thickness, trabeculations, and function—the ability to empty, store, and hold).
5. Both detect reflux (i.e., no advantage).
6. VCUG stages the severity of reflux more accurately.
7. VCUG detects reflux in a duplex system.
8. Nuclear cystograms involve slightly less radiation, but both modalities are safe.

Provocative Imaging—Diuretic Renography

Diuretic renography is the most widely used noninvasive test to determine the severity and functional significance of ureteropelvic urine transport problems in children. Over the years, a wide variety of protocols and techniques have been developed[113]; this has produced significant variability in interpretive criteria and results[114-117] among different nuclear medicine laboratories. Correlation with other techniques, such as pressure flow studies, also has been poor. To improve accuracy and promote standardization of the technique and protocols, three consensus papers have been published from the SFU,[118] the Pediatric Nuclear Medicine Council,[119] and the Ninth International Symposium on Radionuclides in Nephrourology.[120]

The principal radiopharmaceuticals used are technetium 99m diethylenetriamine penta-acetic acid (Tc^{99m}-DPTA), technetium 99m dimercaptosuccinic acid (Tc^{99m}-DMSA), technetium 99m mercaptoacetyltriglycerine (Tc^{99m}-MAG3), and

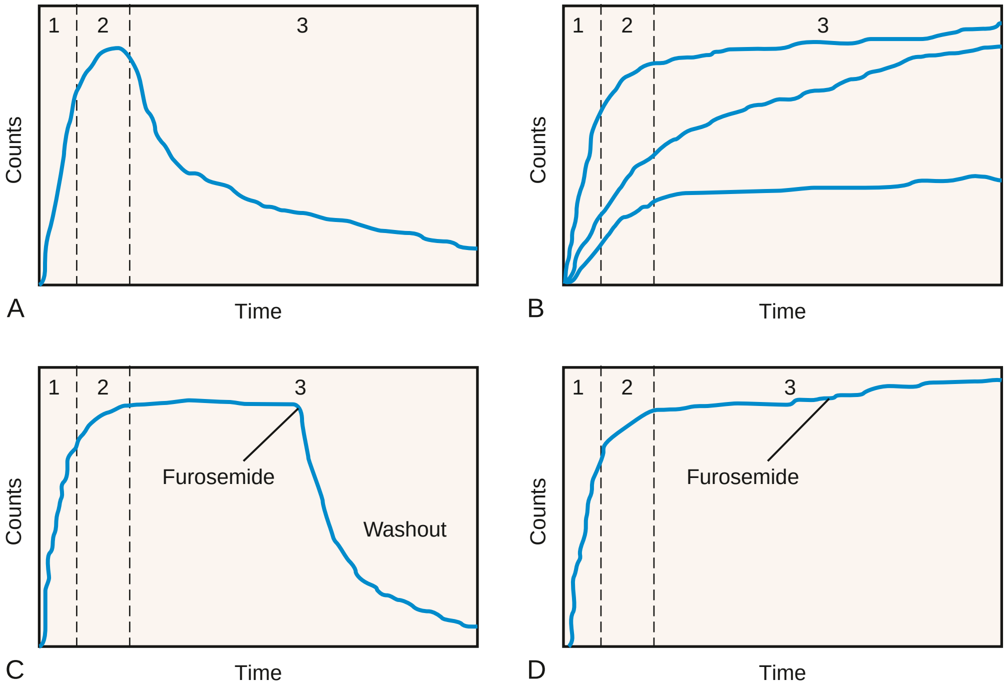


Figure 20-13 Stylized time activity curve in provocative renal renography. **A,** Normal curve shows the three renogram phases: 1 = perfusion phase; 2 = cortical transit phase; 3 = excretion/clearance phase. **B,** Abnormal curves. These curves are typical for obstructive or nonobstructive dilation with accumulation of tracer in the collecting system. Impaired renal function with cortical retention of tracer can produce a similar appearance, although the peak parenchymal activity would be lower than normal *(bottom curve).* **C,** In nonobstructed collecting systems, there is prompt washout of pelvicalyceal activity after intravenous furosemide. **D,** In cases of obstruction or impaired renal function, poor or no washout is seen. (From Roarke MC, Sandler CM. Provocative imaging: diuretic renography. *Urol Clin North Am.* 1998;25:227.)

iodine 123 orthoiodohippurate (I^{123}-OTH). The last agent is not currently available in the United States. The practical choices are MAG3 and DTPA. Current consensus is that MAG3 is the agent of choice.[118,120] The pediatric dose of MAG3 is 50 μCi/kg with a minimum dose of 1 mCi[31] recommended for infants and small children. Hydration is very important so ad libitum oral hydration is encouraged and supervised 2 hours before the start of the study. Normal saline intravenous infusion at the rate of 15 mL/kg over 30 minutes is begun 15 minutes before injection of contrast material. Maintenance infusion at 4 mL/kg/hr is continued for the remainder of the procedure. Choong and colleagues[114] found intravenous volume expansion to be particularly helpful in evaluating infants.

Bladder catheterization is recommended in infants and appropriately small sized children, particularly when reflux is present. A Foley catheter is used for hydronephrosis, and a straight catheter is used for hydroureteronephrosis. The child must remain perfectly still during the testing period. Selective use of conscious sedation may be indicated. Camera collimation and energy vary with the age of the patient and the radiopharmaceutical used. For MAG3, the camera is peaked at 140 kU with a 20% symmetric window. A smaller field-of-view camera should be employed for smaller patients. A renal curve shows three distinct phases (Fig. 20-13): a rapid rise as tracer is delivered to the kidney, a peak region during cortical transfer (60 seconds to appearance of calyceal activity), and prompt decline in activity as tracer is excreted into the collecting system. During the first 60 seconds, completion acquisition is performed at a rate of 1 second per frame. Serial dynamic acquisition is performed at one frame every 10 to 30 seconds. Data are acquired using a 128 × 128 matrix.

From the SFU, differential function is determined from data between 60 seconds and the first appearance of tracer in the calyces (for MAG3, 1 to 2.5 minutes). A C-shaped cortical region of interest that excludes the pyelocalyceal activity is drawn for each kidney. The resulting time activity curve reflects parenchymal function. Normal kidney function is 45% to 55% per side.

A simple recheck of intravenous line position, placement, and patency at the time of radiopharmaceutical and furosemide (Lasix) administration is important. To interpret a provocative renogram properly, the proper dose of furosemide must be delivered to the kidney at the time of maximal pelvic activity. All authors agree with this, but even with standardized protocols, there is still difficulty in achieving it. The most commonly used protocol is that in which furosemide is administered 20 minutes after tracer injection—so-called F_{1-20} protocol. Beginning 15 minutes after injection, the scope images are inspected for evidence of pooling. Sometimes furosemide is injected 15 minutes after tracer—F_{1-15} protocol. It may be necessary in a markedly dilated pelvis to delay injection to 30 to 60 minutes after tracer. According to some authors in equivocal cases, the F_{1-20}-F_{1-15} protocol may need to be used sequentially in the same patient. The written report should include the timing used for a specific patient. The recommended dose of furosemide is 1 mg/kg in infants up to 1 year old and 0.5 mg/kg up to 40 mg for children 1 to 16 years old. It is administered slowly (over 3 minutes) with the midpoint marked on the protocol. A second region of interest is outlined to include the renal pelvis and calyces, but excluding the renal parenchyma.

The most widely used method for quantifying the response to furosemide is to measure the time required to achieve 50% clearance of pyelocalyceal activity in the region of interest. Despite much standardization, the methods for determining this value vary considerably, and no method has been broadly established to date. The main variables are difference

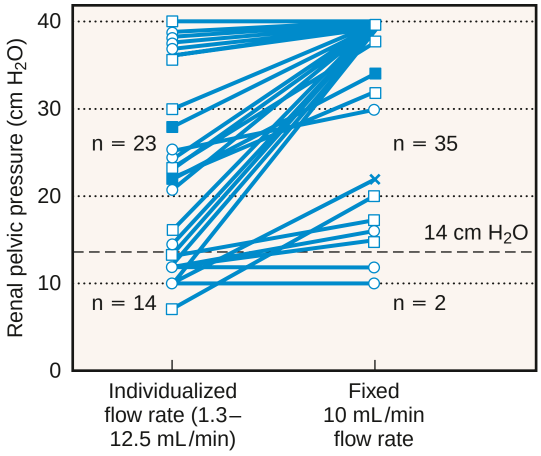


Figure 20-14 Comparative result of pressure flow studies in pediatric patients with possible ureteropelvic junction problems. Patients were tested at the same time with the standardized flow (10 mL/min) versus individual physiologic flow rates. (From Fung LC, Khoury AE, McLorie GA, et al. Evaluation of pediatric hydronephrosis using individualized pressure flow criteria. *J Urol.* 1995;154[2 Pt 2]:671-676.)

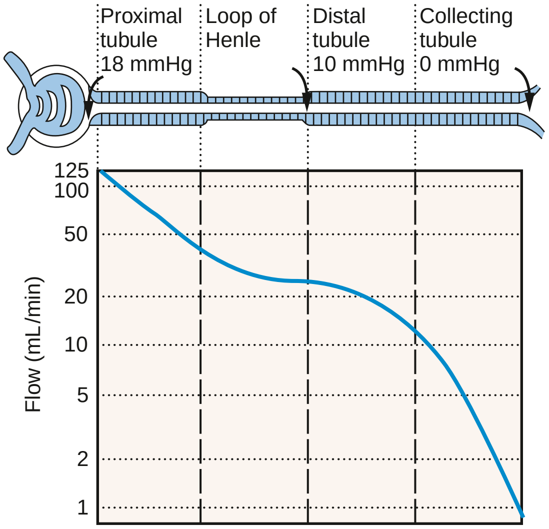


Figure 20-15 Approximate urine flow rates (mL/min) in each section of the nephron. Flow is plotted in a semilogarithmic scale illustrating the significant differences in flow in the proximal versus distal nephron. (From Guyton A. *Textbook of Medical Physiology.* 8th ed. Philadelphia: Saunders; 1991, p 303.)

in when the timing is started, and the mathematical differences in determination of 50% clearance point. Timing may be started when the furosemide is given, or when its affect can be visualized on the activity curve. The former has the disadvantage of disregarding individual response time to the drug, and the latter is subjective, particularly in equivocal cases in which the precise amount of radiopharmaceutical is unclear. Mathematical variation includes linear extrapolation to determine the 50% point on construction of a computer-retrieved exponential best-fit curve.

Most institutions report half-times of less than 15 minutes to be normal and more than 20 minutes as being "obstructed" (see previous discussion). Values between 15 and 20 minutes are equivocal. As mentioned previously, we strongly believe that this single test is not definitive in distinguishing obstructive from nonobstructive cases (see later discussion on correlation).

Perfusion Pressure Flow Studies

Whitaker first described perfusion pressure flow studies[121] in 1973; this test is often called a "Whitaker test." This diagnostic examination, similar to all in the field, has had its proponents and detractors. Similar to provocative renography, the details are crucial, and the casual operator would at best obtain unreliable results and at worst might have a significant complication.

Whitaker's basic idea involved simple concepts: percutaneous access of the renal pelvis, challenge of ureteropelvic urine transport capability by infusion of extrinsic flow (usually 10 mL/min), and simultaneous measurement of intrapelvic pressure (<15 cm H_2O indicating efficiency, 20 cm H_2O indicating inefficiency, and 15 to 20 cm H_2O equivocal). Similar to provocative renography, the technique has been considerably refined to improve its safety, practicality, and accuracy. Fung[123] has introduced several improvements in its use in young children. Early in the evolving experience, Toguri and Fournier[122] outlined overall risk and error problems. Over the years, many of these problems have been addressed.

Accuracy and safety demand control of muscle (skeletal and diaphragmatic) in the prone position. In children, general anesthesia is required, and the prone position requires endotracheal intubation. Accurate placement of the cannula and avoidance of a bloody tap are mandatory. The chances of success are greatly enhanced by simultaneous use of ultrasound (to achieve anatomic position in the renal pelvis) and fluoroscopy (to confirm position), and greatly enhanced by physiologic and anatomic studies.

A serious fault in Whitaker's original proposal was that one flow rate (i.e., 10 mL/min) was used for all sizes of patients. Fung and coworkers[123] showed that this uniform application of a single flow rate resulted in frequent false-positive tests, particularly in younger children (Fig. 20-14). Fung and coworkers[123] proposed a much more physiologic challenge based on individual maximal urine output at the time of that particular test. Figure 20-15 shows diagrammatically urine flow rates (based on a percentage of GFR) in various parts of the nephron. Approximately 90% of filtrate is absorbed in an obligatory fashion in the proximal nephron, and only 10% of GFR reaches the collecting ducts. There the serum osmolality and antidiuretic hormone excretion determine ultimate nephron urine flow rate and osmolality. Under terms of maximum diuresis, urine output equals 10% of GFR; this has been confirmed in the clinical model of nephrogenic diabetes insipidus.

Using this external infused flow rate of 10% of GFR, Fung and coworkers[123] were able to show excellent correlation with results (on the same patients) using internally induced diuresis by intravenous hydration (20 mL/kg/hr of normal saline and furosemide [1 mg/kg]) (Fig. 20-16). This test is more accurate, is more physiologic, and requires only one cannula to be placed in the renal pelvis. Fung and coworkers[123] also were able to prove the important variable relationship between flow rate infused into the renal pelvis either externally or internally (power demand) and ureteropelvic transport rate (power delivery). At low flow (approximately <0.5 mL/kg/hr per kidney), renal pelvic pressures were normal even in systems with severe ureteropelvic inefficiency. Increasing flow rate (either by external infusion or by nephron diuresis) to individual diuretic levels increased the intrapelvic pressures to dangerous levels (>15 to 20 cm H_2O) in inefficient systems, but many dilated systems were able to transport the increased flow effectively (power demands equal

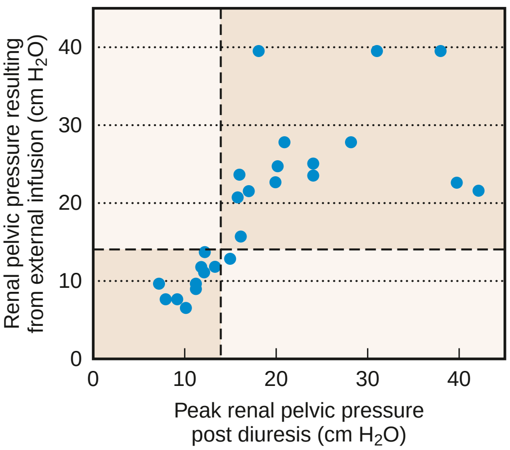


Figure 20-16 Pressure flow studies, individualized external infusion rates versus internal diuresis. (From Fung LC, Khoury AE, McLorie GA, et al. Evaluation of pediatric hydronephrosis using individualized pressure flow criteria. *J Urol.* 1995;154[2 Pt 2]:671-676.)

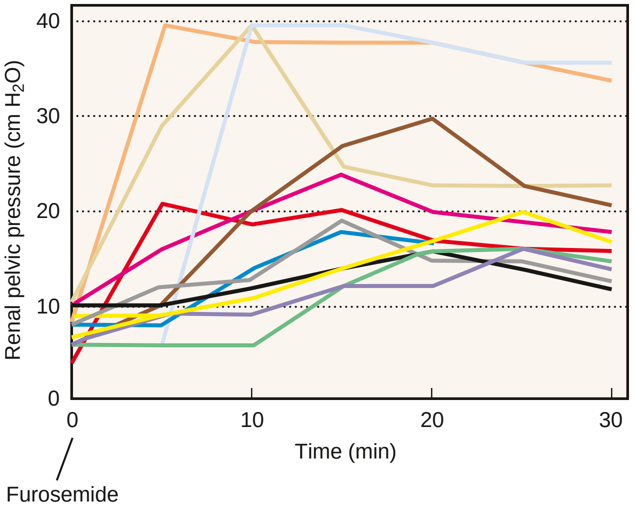


Figure 20-17 Intrarenal pelvic pressure versus time at oliguric and diuretic urine flow rates. (From Fung LC, Khoury AE, McLorie GA, et al. Evaluation of pediatric hydronephrosis using individualized pressure flow criteria. *J Urol.* 1995;154[2 Pt 2]:671-676.)

power delivery), and pressures remained physiologic and safe (<15 cm H_2O) (Fig. 20-17).

Fung and coworkers[123] also showed that increasing flow rates above "individual" physiologic levels increased intrapelvic pressures in all patients. Finally, Fung's work provided the key link between renal blood flow (as measured by Doppler resistive index—see later discussion) and renal pelvic pressure in pediatric patients.[53]

Progressive increases in flow rates presented to the renal pelvis by external infusion increased resistive index (decreased diastolic renal blood flow) in an approximately parallel linear fashion (see diagram) in all patients. It established that renal pelvic pressures less than 15 cm H_2O are low and physiologically safe, whereas pressures greater than 15 cm H_2O progressively reduced renal diastolic blood flow, confirming animal model studies. This allows a different interpretation of severity. The following generalizations can be made:

1. In complete congenital ureteral obstruction (ureteral atresia), a multicystic dysplastic kidney results, and this is not a diagnostic dilemma.
2. All UPJs and ureters have a rate-limited ability to transport urine (power delivery). External infusion over this rate increases pelvic pressure and decreases diastolic renal blood flow.
3. The rate-limited ureteral urine delivery (power delivery) is best expressed as a percentage of normal GFR for the size (surface area) of the child.
4. Maximal ureteral (and ureteropelvic) power delivery rate is at least 10% of the GFR for both kidneys, and that is at least two times as great a flow as the ureter would encounter (maximum diuresis of 10% of GFR for one kidney).
5. Our studies have shown that GFR and bladder volumes mature in children at the same rate. Logically, maximal ureter urine delivery rates also mature at the same rates.
6. At low urine flow rates (<1 mL/kg/hr), renal pelvic pressure remains normal even in severe hydronephrosis with major transport inefficiency (no previous surgery).
7. At maximum diuresis (10% of normal single kidney GFR), in more than 99% of children, ureteral delivery rate is equal or extremely minimal, or transient pelvic dilation occurs. In minimal hypoplastic adynamic segment, maximal ureteral urine transport rate (ureteral power delivery) does not quite equal nephron urine output (power demand), and dilation (often persistent) occurs. The collecting system is sufficiently elastic, however, to accommodate the imbalance in flows, and renal pelvis pressure remains low and safe, and renal blood flow, renal parenchymal volume, and renal function are maintained. The physiologic challenge to these marginal ureters decreases in the first few years of life as GFR matures less rapidly, maximal concentrating ability increases (600 to 1200 mOsm), and diet changes from completely liquid to liquid and solid.

Computed Tomography Urography with Ureteral Fluoroscopy

If perinatal ultrasound, postnatal ultrasound, and voiding cystourethrogram suggest a significant upper urinary tract congenital anomaly, our current imaging method of choice at Clark-Morrison Children's Urological Center at UCLA is CT urography with optimal ureteral fluoroscopy. It gives us all the information that we need to maximize the safety, selection, and success of management strategy in a single examination. In young children, CT urography requires conscious sedation (also frequently used in provocative renography). It allows an accurate assessment of the significance and severity of UPJ problems and precise preoperative anatomy and physiologic significance in a single examination. More specifically, advantages can be summarized as follows:

1. The severity and significance of UPJ urine transport inefficiency can be assessed by objective evaluation of the presence and measurement of the severity of secondary renal parenchymal ischemic atrophy (see previous section).
2. The presence of renal scarring can be simultaneously detected.
3. Renal function can be assessed accurately but subjectively.
4. The anatomy of aberrant vessels, secondary kinks, and adhesions is accurately diagnosed.

5. The exact site of hypoplastic adynamic ureteral segment using simultaneous ureteral fluoroscopy can be identified at proximal (UPJ), distal (ureterovesical junction), middle, or occasionally multiple sites.
6. Retrocaval ureters (0.5% to 1%) are exactly and accurately diagnosed.
7. The presence of associated renal anomalies—horseshoe, duplex, and ectopic (fused or unfused) kidney—is detected.
8. It provides an accurate test of anomalies such as ectopic ureterocele included in the differential diagnosis.
9. The cost of investigation is comparable to all other single tests and less expensive when multiple modalities are used.
10. Using non-ionic osmotic contrast media, safety is comparable to other techniques.
11. Radiation exposure is comparable to a standard intravenous pyelogram.

Novel Applications of Spiral Computed Tomography Technology—Renal Parenchymal Measurements

Attempts of objective renal parenchymal quantification using ultrasound have been inconsistently successful because of the dilation of the renal pelvis relative to the parenchyma. Cost and associates[124] showed poor correlation between the renal length and the parenchymal area in hydronephrotic kidneys. They suggested that the ratio of the pelvic calyceal distance might be a better predictor of clinical outcome. Pruthi and coworkers[125] showed in hydronephrotic kidneys that renal length correlated poorly with renal function because it overestimated the functional area of the kidney. These authors also pointed out that accurate quantification of ultrasound area is difficult to perform, is subject to significant interobserver bias, and is time-consuming.

We have developed a completely automated method of measuring renal parenchymal volume. Beginning with a specific imaging protocol, the electronic data from the CT scanner is transferred to a computer workstation, which reconstructs the kidney in three dimensions. Using the Hounsfield unit and volume information (voxel) of each image slice, our novel computer algorithm precisely discriminates the renal parenchyma from all other structures in the abdomen (within 5% actual measurement of computer calculated volume). We have been extremely successful in measuring parenchymal volumes in normal kidneys, and we have applied this technology to hydronephrotic kidneys.

Anatomic Studies—Retrograde/Antegrade Pyelogram

Studies from the Hospital for Sick Children in Toronto and Boston Children's Hospital indicate that in 4% to 5% of cases, detrimental confusion can occur intraoperatively and postoperatively because of failure to establish the exact site of the hypoplastic ureteral adynamic segment and to make an accurate preoperative diagnosis of right retrocaval ureter. Although many prominent institutions, such as Boston Children's Hospital, continue to use retrograde or antegrade pyelography, others, including National Children's Hospital in Washington, D.C., rely entirely on nuclear scans, designed primarily to determine physiologic significance, but with careful technique also yielding anatomic details. A key point in this ongoing debate is the accuracy of separating hydronephrosis from hydroureteronephrosis in one's own practice setting. From a personal perspective, we insist on a good preoperative anatomic imaging study in all operative cases. This study is particularly important if a very selective anatomic exposure, such as posterior lumbotomy approach, is to be used. At Clark-Morrison Children's Urological Center at UCLA, we have had three cases (one retrocaval ureter and two midureteral adynamic segments) in which success would have been compromised had we not employed routine preoperative anatomic imaging. Our current method of choice is ureteral fluoroscopy done in conjunction with CT urography (see earlier section).

PRENATAL MANAGEMENT

Since the routine application of maternal-fetal ultrasonography, virtually every pediatric urologist in the world has acquired a new type of patient—the pregnant mother. As mentioned in the section on diagnostic testing, accurate prenatal diagnosis must determine the presence, severity, and progression of the lesion. Accurate pathologic anatomy and physiology must be rendered as soon and as accurately as practically possible. Emphasis must be on family education, term counseling, and presentation of options.

Evaluation must include the following:

1. The significance of detectable urinary tract dilation in utero varies significantly from incidental to catastrophic.
2. An excellent prognosis is more common than a good prognosis, which is more common than a poor prognosis, which is more common than a catastrophic prognosis.
3. Kidneys are paired organs, and unilateral disease (with a contralateral kidney) never constitutes immediate life-threatening disease, and in utero invasive procedures or early delivery is never indicated.
4. Fetal renal pelvis size does not correlate with significance. Dilation of 3 to 11 mm (seen at 26 to 28 weeks of gestation) occurs in 18% of fetuses and very seldom results in operative problems postnatally. Dilation of more than 12 mm resulted in postnatal surgery in 34% of patients managed in a very conservative group. Dilation greater than 20 mm is clinically significant, but does not always require postnatal operative intervention. If postnatal operative intervention is required, it is usually very successful with few long-term sequelae.
5. In cases of very severe (SFU grade IV) unilateral lesions leading to unilateral renal loss with a normal contralateral kidney, an excellent quality and length of life can be achieved with one kidney. Highly intelligent people daily voluntarily donate one of their kidneys to another person.
6. The concept of a "hopeful" versus "hopeless" kidney must be explained to the family. A hydronephrotic kidney (even severely) is hopeful and is capable of delivery of future long-term meaningful renal function. A severely hypoplastic kidney is hopeless. It is important also to explain timing and accuracy of establishing distinguishing diagnosis.
7. In establishing perspective, it is important to remind families that billions of people have lived on the earth, and that all have encountered or will encounter significant disease.
8. In cases of bilateral hydronephroses, the prognosis primarily depends on the status of the favorable kidney. Frequently in bilateral UPJ obstruction problems, there is significant asymmetry in severity.
9. Some cases have obvious indications of severity. These include bilateral (or solitary kidney) dilation of greater than 20 mm, bilateral evidence of hypoplastic dysplasia, progressive bilateral dilation with ultrasound evidence of oligohydramnios, and pulmonary hypoplasia.
10. Perinatal imaging is not 100% accurate.

Practical prenatal management choices include the following:

1. Following 20- and 28-week ultrasound scans, carry to term without further prenatal ultrasound with postnatal ultrasound and VCUG; no recommended changes in obstetric management.
2. Carry to term with no further ultrasound; changes recommended in obstetric management, and VCUG and postnatal ultrasound strongly recommended. For hydronephrosis with neural tube defect, elective cesarean section without trial of labor indicated when fetal maturity confirmed, and in significant sacral coccygeal teratomas.
3. Carry to term with serial ultrasound scans; bilateral cases with best kidney well visualized and SFU grade III or better. In other words, the best kidney is not hypoplastic and has normal renal parenchyma; amniotic volume is normal and is reconfirmed serially.
4. Carry to term while checking lung maturity with sphingomyelin ratios; consider early delivery, and the use of steroids.
5. In utero intervention at term after second evaluation.
6. Terminate pregnancy.

INTRAUTERINE INTERVENTION

Since its debut accompanied by national magazine coverage, intrauterine surgery has had limited applications in terms of total number of patients successfully treated on a worldwide basis. Careful detailed long-term follow-up studies at Boston Children's Hospital indicated that only 20% of patients with prenatally detected urinary dilation are candidates for such treatment. Nevertheless, centers of excellence, such as the Fetal Treatment Center at the University of California in San Francisco, remain progressive, committed, innovative, and able to publish significant feats of technical excellence.

Families considering such treatment should be aware of reported complication rates of 45% associated with shunting procedures. These are from reporting centers. It is safe to assume that complication rates in nonreporting centers are even higher. Complications include preterm labor, hemorrhage, chorioamnionitis, urinary ascites, catheter migration, and catheter failure.[36] The medicolegal status is complicated and frequently concentrates on "rights" of the fetus and mother. Ethical dilemmas involving responsibility are complex. Controlled studies show that long-term benefits are lacking. Tertiary medical centers with the emotional commitment, technical expertise, and experience would have problems not treating suitable patients. The decision is often made whether the mother and fetus are referred or not to such a committed center.

TERMINATION

In our opinion, no single subject divides Americans more than therapeutic abortions. Physicians and families, for religious, personal, and philosophical reasons, often have dramatically opposed views. The widespread use of this procedure may affect the future of pediatric urology more than any other future event. Use of therapeutic abortion is more common in European countries and has already affected practice patterns. Paradoxically, it is often most commonly used in countries whose citizens are primarily Roman Catholic (e.g., France) despite the Church's traditional, steadfast, and total opposition. More recent presentations at international meetings have indicated routine use of late-term abortion for severe genitourinary problems. We believe that the physician should declare his or her personal beliefs to the family. Nevertheless, there are extreme circumstances in which neonatal life is essentially impossible (e.g., bilateral hypoplasia, severe oligohydramnios, and pulmonary hypoplasia), in which termination, whether therapeutic or spontaneous, is inevitable.

POSTNATAL MANAGEMENT

Careful physical examination to include or exclude all conditions or widespread differential diagnosis is indicated. These conditions include myelodysplasia, sacrococcygeal teratoma, cloaca and urogenital sinus problems, lower tract dysfunction with imperforate anus, prune-belly syndrome, and hydrometrocolpos. Lower tract problems including anterior and posterior urethral valves, bladder diverticulum, ectopic ureterocele, or ectopic ureter and primary reflux are included or excluded by VCUG (see earlier section on VCUG versus nuclear cystogram). Postnatal ultrasound is done at 3 to 5 days of age (e.g., after 48 hours) except in cases where VCUG shows a significant lower tract problem, and management has to be advanced because of the severity of the pathology.

After VCUG and postnatal ultrasound, patients are assigned to various management groups as follows:

1. Examination, VCUG, and ultrasound—all normal.
   Many authors stop further follow-up at this point.
   Other authors suggest a second ultrasound 3 to 7 months later.
2. Examination normal, VCUG shows primary VUR, ultrasound shows hydronephrosis.
   Patients are followed as outpatients on prophylactic antibiotics, and primary VUR is managed appropriately.
3. Examination normal, VCUG shows other primary disease such as posterior urethral valves, ultrasound shows hydronephrosis.
   Appropriate management is instituted.
4. Examination normal, VCUG normal, ultrasound shows one normal kidney and one hydronephrotic kidney.
   Defer imaging to at least 1 month of age, or longer if low birth weight.
5. Examination normal, VCUG normal or shows minimal reflux, ultrasound shows mild bilateral hydronephrosis.
   Favorable prognosis (SFU grade II or better).
   Treat as above.
6. Examination normal, VCUG normal or shows minimal reflux, ultrasound shows solitary or bilateral hydronephrosis with the better kidney SFU grade III or worse, particularly if both kidneys are SFU grade IV.
   Serial daily serum creatinine beginning at day 2 of life.
   If renal function worsens, treat as neonatal renal failure (see subsequent discussion).

SELECTION OF FURTHER IMAGING

As detailed earlier, the selection of further imaging is wide and confusing to the patient and occasionally to the physician. The physician should select a technique with a demonstrable level of expertise, experience, and consultation. The physiologic significance should be assessed by one of the following:

1. Provocative nuclear renography
2. Split renal function
3. Pressure flow studies

4. Objective evaluation of renal parenchymal atrophy by CT urograms

If operative intervention is considered, we strongly suggest obtaining imaging with anatomic detail by:

1. Intravenous urography with contrast media (currently unpopular but in our opinion is often still very useful)
2. Antegrade or retrograde pyelogram
3. CT urography

DECISION, TIMING, AND NECESSITY OF SURGERY

Since the advent of maternal-fetal ultrasound and the introduction of time bias, opinions have been and continue to be partially split and controversial regarding the decision, timing, and necessity of surgery.[126]

SURGICAL TREATMENT

Similar to imaging, modern advances have resulted in many surgical options for correction of a pediatric UPJ. The main decisions that have to be made when surgery is indicated are the following:

1. Repair by excision of hypoplastic ureteral adynamic segment and reanastomosis or by incision and splinting
2. Open surgical technique versus primarily endoscopic
3. If open technique, determination of the operative approaches
4. Use of splints or proximal diversion (external versus internal), or both
5. Choice of suture material with open technique
6. What type of endoscopic repair to employ—antegrade versus retrograde, and direct vision versus fluoroscopic
7. Use of a laparoscopic/robotic-assisted repair or not

Open versus Endoscopic Technique

Figenshau and Clayman[129] indicate that at the present time "neonates and infants are not good candidates for endourologic intervention." The technical problem can be insurmountable, the radiation exposure can be extensive, and two and perhaps three anesthesias can be needed—all major obstacles to endoscopic treatment in neonates, infants, and small children. Open surgery remains the management of choice compared with an endourologic approach. In older preadolescent and adolescent children, the choice is more controversial.

Approaches for Open Pyeloplasty

Posterior Lumbotomy

Posterior lumbotomy is our approach of choice in infants, smaller children, and lean older preadolescents with a normally located operative kidney. The muscle splitting rather than muscle cutting makes it almost a minimally invasive procedure. The posterior and in the crease line location has a cosmetic advantage. In smaller children, the UPJ practically can be brought out to almost the level of the skin, giving outstanding opportunities for application of surgical optical magnification. Aberrant lower pole vessels are easily seen and managed. It is, however, a "bomb-sight" incision, requiring precise location of the UPJ, and should not be used on ectopic kidneys or in very inferiorly located operative sites. In our experience, posterior lumbotomy should be avoided in older children or significantly obese children.

We use a Foley catheter with a Y connector for infusing color confirmation (see later section on use of splints). Endotracheal intubation, relaxation, ventilation, and *no nitrous oxide* are mandatory. The child is flexed using the anatomic location of the kidney as the midpoint, and we use the kidney rest and flexion capability of a Skytron 6000 (Skytron, Grand Rapids, MI) surgical table. The child is placed in a prone position with suitably sized transverse thoracic and midthigh rolls. A transverse skin incision is made just under and parallel to the 12th rib with one third of the incision over the paraspinal muscle and two thirds lateral to the skin. The subcutaneous tissues are extensively mobilized to permit a longitudinal incision over the midlumbodorsal fascia and paraspinal muscle. The three circular muscles (external oblique, internal oblique, and transversus abdominis) are slid laterally to separate from each of three longitudinal muscles (erector spinae, quadratus lumborum, and psoas). We find bipolar cautery invaluable.

Closure is with a single muscle fascia layer bringing the lumbodorsal fascia back together again. We use interrupted modified figure-of-8 (Maxon, Ethicon) sutures for this. We have often done bilateral procedures successfully under the same anesthesia without position changes or redraping. Pain is minimal, morbidity is reduced, and mobilization is almost immediate.

Lateral Flank Approach

The classic traditional approach for pyeloplasty is the lateral flank position. The advantage is the greater flexibility with exposure if anatomic details are unusual and not well demarcated. The disadvantage compared with the posterior lumbotomy is that muscles are cut, creating increased pain and a less favorable cosmetic appearance. If a bilateral approach is desired, the patient needs to be repositioned and redraped.

Anterior Approaches

Primarily extraperitoneal approaches are used in anterior approaches. A subcostal incision and an extraperitoneal approach are favored by some authors. Bilateral approaches can be performed without repositioning or redraping. Similar to a subcostal flank incision, it is a muscle-cutting incision. Other anterior extraperitoneal approaches include the Gibson incision for ectopic or horseshoe kidney.

Use of Splints or Diverting Nephrostomy

We currently strongly prefer temporary internal splints (double-J ureteral stents). An abdominal radiograph showing kidneys, ureters, and bladder is obtained preoperatively, and the bladder to the renal pelvis distance is measured. A suitable length double-J Silastic splint (Cook Catheters, Cook Medical, Bloomington, IN) 10 to 26 cm (2-cm increments) is selected. In some smaller-sized patients, a 3F size is used. The bladder is catheterized with an appropriately sized Foley catheter connected to a three-way Y connector. One port of the Y connector is attached to the drainage port of the Foley catheter. One arm of the Y is attached to a bladder infusion drainage (normal saline with 1 mL of indigo carmine), and the other arm of the Y is attached to a drainage bag. The infusion port is turned "off" during initial phases of the operation so that urine output can be measured. At the appropriate point, the drainage bag port is turned "off," and the colorimetric infusion drainage fills two thirds of the bladder (amount infused [mL] = [age + 2] × 3). An 0.018-inch diameter hydrophilic guidewire and the ureteral splint are carefully guided to the bladder until an efflux of blue infusate is observed, confirming the intravesical position of the

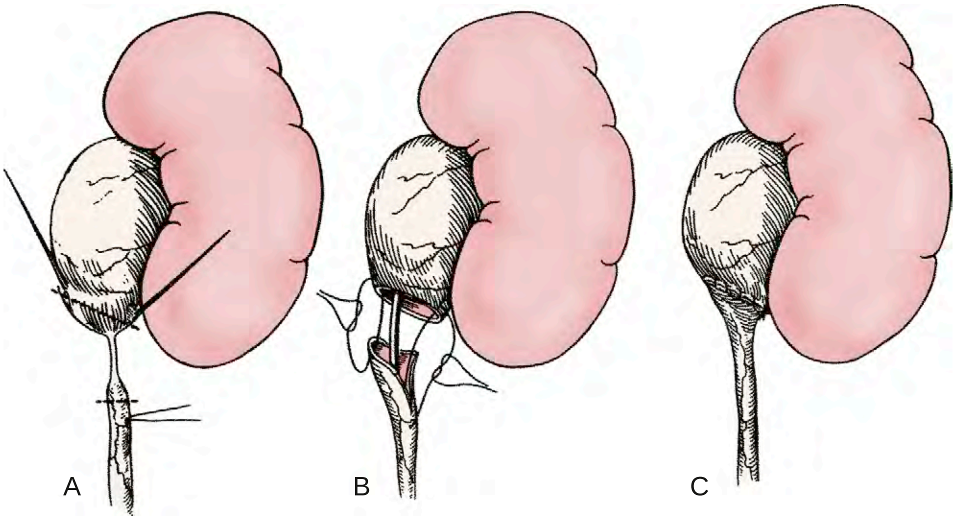


Figure 20-18 Schematic depiction of standardized technique of open pyeloplasty as proposed by Hynes and Anderson. **A,** Lines of cuts to excise the hypoplastic adynamic ureteral segment. **B,** Ureteral spatulation to face the renal parenchyma and placing preliminary sutures. **C,** Completed procedure. (From Novick AC, Streem AB. Surgery of the kidney. In: Walsh PC, Retik AB, Vaughan ED, et al, eds. *Campbell's Urology.* 7th ed. Philadelphia: Saunders; 1998: 3044.)

inferior double-J splint. In this manner, we avoid catheterizing the ureter just before or during surgery. The proximal double-J loop is placed into the renal pelvis under direct vision.

The Foley catheter is removed at 24 hours, and the dressing is removed at 48 hours, at which time discharge is routine. Our experience with this technique over many years has virtually eliminated ureteral leaks, early operative obstructions, and risk of anuria in bilateral cases. Retrieval is at 6 weeks postoperatively with fluoroscopy or cystoscopy. Other authors have reported similar reliable, reproducible, and dependable results.

At the Hospital for Sick Children in Toronto, a second alternative method is catheter drainage. A third alternative is to use no splints or catheters at all. Many series report excellent results with such a protocol. The use of a percutaneous malecot nephrostomy tube and temporary splint is a technique we used for hundreds of cases decades ago, and this technique is still advocated by some physicians. We now believe this technique is outdated, however. The choice of splints does not change in our hands when faced with pyeloplasty on a solitary kidney or repeat procedures.

Open Technique of Pyeloplasty

The standardized open technique is shown in Figure 20-18. We use the dismembered technique of Hynes and Anderson with the excision of the adynamic hypoplastic ureteral segment and reanastomosis in 98% of our cases. The ureteral incision is angulated (inferior adjacent to inferior pole) and spatulated so that the open end of the divided ureter lays over the open renal pelvis. We always have at least a 6-mm (diameter) anastomosis. We prefer interrupted 6-0 or 7-0 (Maxon or PDS) sutures with the adjacent sides anastomosed first. The double-J splint is carefully placed just after the midpoint of the anastomotic phase of the operation. A solitary kidney or reoperative case does change our technique. We mobilize the kidney more in a reoperation to permit inferior renal location and decreased anastomotic tension.

Previously, we have used 6-0 Vicryl or Dexon sutures, but now we strongly believe Maxon and PDS sutures have better tissue handling capability and longer life (but still absorbable). Other alternatives include Foley V-Y plasty and the spiral flap of Culp and Scardino, all of which have their advocates and perhaps special individual anatomic indications. With use of a preoperative CT urogram, we are usually aware of aberrant vessels preoperatively.

Endourologic Options in Children

Percutaneous and endoscopic techniques were developed in the 1980s primarily for nephrolithiasis. By the mid-1980s, reports appeared concerning techniques to repair UPJ urine transport problems in adults and subsequently in children.[127] The basic principle involved marriages of the old and the new. The old concept was the full-thickness incision of the hypoplastic adynamic segment followed by prolonged stenting and drainage to allow regeneration of adequate caliber around the stent. The concept was first described by a French urologist Albarran[6] and popularized by Davis and colleagues.[128] The new concept was the innovative minimally invasive technique of delivering the incision and subsequent stenting.

Selection of Patients

Even strong experienced advocates do not recommend these procedures in neonates, infants, or young children.[129] In preadolescent children, the choice is more controversial. In adolescents, the anatomy is similar to adults. Massive hydronephrosis or crossing aberrant vessels or both in multiple reports decrease success. Preoperative imaging may direct the safest place for ureterotomy. Figenshau and Clayman[129] and other authors empirically place the cut in a lateral position. Long avascular strictures, total obliteration of the lumen, and periureteral fibrosis are contraindications for the procedure.[127,130-134]

Success of Endopyelotomy

The success rate of endopyelotomy seems to be independent of the approach (retrograde or percutaneous antegrade) (Table 20-2). Similarly, the type of incision, whether using Accucise (Applied Urology, Laguna Hills, CA), a balloon with

Table 20-2 **Outcome of Endopyelotomy**

Risk Factors	Percent Successful
Vessels absent, low-grade hydronephrosis	90
Vessels absent, high-grade hydronephrosis	74
Vessels present	33
Vessels present, high-grade hydronephrosis	30

From Van Cangh P, Nesa S, Galeon M. Vessels around the ureteropelvic junction: significance and imaging by conventional radiology. *J Endourol.* 1996;10:111.

fluoroscopic control; laser incision; or a hot or cold knife, seems to have little effect on the result. The results of endo(uretero)pyelotomy in children are discussed in a previous section. In both techniques, the actual incision is made with an Accucise balloon. A retrograde pyelogram is performed minutes before to outline the hypoplastic adynamic segment. The balloon position is confirmed fluoroscopically in the retrograde technique and combined with nephroscopy in the dual approach.

In younger children, two guidewires are secured. The cutting wire is positioned laterally empirically in primary cases and individualized according to renovascular CT findings in secondary cases. The balloon is positioned with the midportion straddling the UPJ. The balloon is inflated to 1 mL with contrast material to confirm the balloon and cutting wire position. The balloon is then inflated to full volume of 2 mL while electrifying the cutting wire with 50 to 75 Hz of pure cutting current. This takes only a "few seconds," and the cut is confirmed fluoroscopically by disappearance of the waist. In the dual approach, the UPJ is opened, the balloon is kept expanded for 10 minutes for tamponade and then removed, and an appropriate stent (48F to 7F) is positioned by fluoroscopic and possibly nephroscopic control. In the combined technique, a nephrostomy tube is left for days. A nephrostogram is used to evaluate drainage and presence of extravasation. If both are satisfactory, the nephrostomy tube is removed under fluoroscopic control to avoid dislodging the splint.

Balloon dilation of the UPJ also has been reported in children, primarily in infants and young children. It is minimally invasive and appealing because of the minimum risk of bleeding. The technique is simple. A 0.035-inch diameter straight or hydrophilic-coated guidewire is passed up the ureter and coiled in the renal pelvis. The scope is withdrawn, and a 5F angiographic catheter is passed into the pelvis. The wire is withdrawn, and fluoroscopic imaging is obtained. A 0.035-inch Benston wire (Cook Medical, Bloomington, IN) is passed, and the angiographic catheter is exchanged for a dilating balloon catheter (12F to 24F), which is positioned, confirmed, and inflated for 3 minutes. A 4.8F to 7F stent is placed and left for 6 weeks. The success rate was 63% (follow-up to 23 months).

MINIMALLY INVASIVE SURGERY IN CHILDREN

Laparoscopic Pyeloplasty

The trend toward minimally invasive surgery can be seen throughout urologic surgery. With improved optical resolution, image digitalization, and miniaturization of endoscopes and laparoscopes, open pyelolithotomy and ureterolithotomy are no longer the standard of care for stone disease. Minimally invasive surgery has expanded beyond the management of calculi. A survey of practicing adult urologists indicated that 43.5% of respondents would consider Acucise as a first-line treatment for UPJ if no crossing vessel was found. If a pyeloplasty was considered, 34.3% would choose a laparoscopic approach versus an open one.[58]

The movement toward minimally invasive surgery is also seen in pediatric urology. Diagnostic laparoscopy for a nonpalpable testis has been well established. Laparoscopic orchidopexy for an intra-abdominal testis and laparoscopic varicocelectomy are routinely performed by pediatric urologists.[135] Laparoscopic approaches to extirpative procedures, such as orchiectomies, nephrectomies, and partial nephrectomies have gained popularity.[136] Laparoscopic pyeloplasty in children is being performed at leading academic centers.[135,137] Through either a transabdominal or retroperitoneal approach, the advantages of decreased postoperative analgesia, shorter hospital stay, and improved cosmesis have been well established in adults and are shown in pediatric patients as well.[138,139]

Laparoscopic pyeloplasty in pediatric patients is technically demanding. The steep learning curve is attributed mainly to the requirement for intracorporeal suturing and knot tying. The pediatric laparoscopic surgeon is limited to instruments with 3 degrees of freedom and a two-dimensional view of the operative field. Laparoscopy relies on the surgeon to be comfortable with parallax manipulation of the surgical instruments. Because the fulcrum of the laparoscopic trocars is at the plane of the skin/fascia, counterintuitive motions of surgical instruments (i.e., extracorporeal downward deflection of an instrument results in intracorporeal upward deflection) are difficult to master for surgeons who do not perform laparoscopic procedures routinely. Laparoscopic pyeloplasty requires a set of skills that makes this procedure a formidable challenge for pediatric urologists.

Robotic Surgery

Robotic-assisted pyeloplasty attempts to overcome the technical hurdles of laparoscopic surgery. One of the authors (W.C.F.) routinely uses the daVinci Robotic System (Intuitive Surgical, Sunnyvale, CA) in a minimally invasive approach to pyeloplasty. Robotic pyeloplasty directly mimics our open technique. The UPJ is exposed transabdominally through a retroperitoneal or transmesenteric approach. Complex intracorporeal movements, such as dissecting, suturing, and knot tying, are easily mastered.[140] The daVinci system has 15 times optical magnification in a three-dimensional viewing environment. The robotic instruments are placed through 5- or 8-mm trocars allowing for 6 degrees of freedom.[141] The pyeloplasty is performed in the same manner as first described by Anderson and Hynes[21] in 1949. A renal pelvis stay suture is introduced extracorporeally and can be repositioned easily during the ureteropelvic anastomoses. Finally, a 4.7F double-J ureteral stent is easily placed intraoperatively through a 14-gauge intravenous catheter punctured into the abdominal wall under direct vision. The short-term outcomes of our robotic-assisted pyeloplasties (e.g., decreased hydronephrosis, preservation of renal function) are indistinguishable from our open series. The long-term efficacy of this approach is not yet supported by the literature, however.

We contend that robotic surgery should be considered a direct translation of open surgery and does not represent an evolution of laparoscopy. Because robotic surgery does not use laparoscopic skills (as described earlier), it represents an extension of the "open surgery" branch of the surgical tree. The major drawback of robotic surgery is the lack of tactile sensation or feedback for the surgeon. Instead, robotic-assisted surgery must use visual clues surrounding the operative site to adjust for the lack of this sensation.

COMPLICATIONS OF SURGERY

Parents must be informed about potential, general, and specific complications of the procedure. For prevention of general complications, several safety measures must be followed meticulously. First, all of these procedures require endotracheal anesthesia. We do not perform such procedures (even balloon dilation) with a laryngeal airway. In open procedures (particularly posterior lumbotomy), we avoid nitrous oxide to minimize the dilation of the intestinal tract. Any procedure requiring position changes (e.g., posterior lumbotomy pyeloplasty) requires stethoscope auscultation confirmation of good airway entry into both lungs after each position change. In small infants, we either use a central line (internal jugular or subclavian) or have two well-performing peripheral intravenous access lines. An appropriate-sized cautery plate is positioned, and great care is taken not to get it wet during the preparation of the wound. In positioning patients, great care must be taken to ensure no pressure points are compressed. Irrigation instilled into the urinary tract for any open endoscopic procedure must be nonelectrolyte (i.e., water).

The complications of surgery for UPJ problems are similar regardless of whether the approach is intraluminal, extramural, open, or endoscopic. Although certain techniques have a predilection for certain complications, there seems to be little doubt that some techniques generally have higher complication rates than others. Similar to any other operation, complications can be general or specific.

Pulmonary complications can be minimized by using endotracheal anesthesia even for endourologic procedures.[129] Because many of these procedures involve an unusual position, air entry in *both lungs* must be confirmed before and after position changes. Significant hemorrhage occurs primarily from adjacent aberrant vessels. Accurate preoperative and intraoperative diagnosis minimizes these complications.

For endourologic procedures, the prospective patient (or parent) is advised regarding the following:

1. Ureteral imaging techniques for preoperative diagnosis.
2. We advise CT urography.
3. Most incisions are made laterally.
4. Particular care is taken in anomalous kidneys.
5. “Plan B”—alternative emergency open intervention with catastrophic hemorrhage—is established before the procedure.
6. Prophylactic and therapeutic preoperative and intraoperative antibiotics minimize infection.

Specific Complications

Obstruction

Obstruction occurs primarily at the operative site, but also occurs at the ureterovesical junction. Obstruction occurs most commonly in balloon dilation in children (rate of 20%).[129] In collective series of endopyelotomy (total of 86 patients), the overall failure or complication rate was 14%. Distal ureterovesical problems are more common in endoscopic procedures involving multiple instrumentation of the ureterovesical junction. A series of 70 neonates with open pyeloplasties at the Children’s Hospital of Philadelphia had no postoperative obstruction. Other authors report a postoperative obstruction rate of 0.9%[142,143] In our experience, postoperative (after open pyeloplasty) ureterovesical urine transport problems also involve multiple perioperative ipsilateral ureteral instrumentation.

Leaks

Leaks into the retroperitoneum and wound from nonstented open pediatric pyeloplasties have been reported. Reoperation after prolonged hospitalization can occur in 4.8%.[144] This problem has been virtually eliminated in our experience (and others) by routine use of internal double-J stents. Urine leakage into the thorax occurs primarily with antegrade endourologic procedures.[129]

Renal Destruction and Renal Failure

The rate of renal destruction and renal failure depends on the severity of the renal parenchymal damage before the operation. Very marginal kidneys are subjected to repair in hopes that meaningful renal function will result. Virtually all more recent endourologic reports show significantly decreased results in massive hydronephrosis with marginal function. Probably similar trends exist among open surgical results.

Ureteral Damage with Loss of Patency, Continuity, and Significant Loss of Length

Ureteral damage is one of the most serious complications because (1) the kidney is completely obstructed, and (2) the kidney’s survival is in jeopardy unless there is a proximal nephrostomy, which is subject to displacement, infection, and calculi. Extravasation and periureteral fibrosis are also common, and, as to be expected, repair is difficult. These complications have been seen or reported with all types of repair and represent significant ischemic ureteral injury. One of the authors (B.M.C.) has been able to avoid these challenges by extensive exposure, release, dropping of the kidney, and elevation of the ureter without placement of bowel interposition. In very severe cases, bowel interposition or autotransplantation is indicated.

RESULTS OF MANAGEMENT

In this section, we review the results of management of UPJ problems in children by the following methods of treatment: intrauterine intervention, postnatal serial observation, standard open pyeloplasty, endopyelotomy, and ureteropelvic dilation. Laparoscopic pyeloplasty has been reported in children, but multiple center reports of a reasonable number of patients are unavailable to make a meaningful judgment.

Comparison of results is difficult for various reasons. First, there is not a standard method of premanagement staging of severity. The most widely used criteria are the SFU classification for hydronephrosis and split GFR based on nuclear medicine studies. Second, there is no standard follow-up interval, such as 5 or 10 years. Finally, in contrast to the oncology field, where survival and disease-free survival are easily comprehended and documented, there are no standard criteria of success.

Intrauterine intervention, as explained earlier, is applied only to more severe bilateral (or solitary) kidney problems with oligohydramnios and pulmonary development problems. The results must be compared with an oncology series, which includes only the highest grade and highest stage patients. Also, these procedures are applied to all causes of hydro(uretero)nephrosis. The results of the international fetal surgery registry showed that 41% survived.[36] Pulmonary hypoplasia was the most common cause of death in treated and untreated patients. The procedure-related death rate was 4.6%. The authors reported the most favorable results in posterior urethral valves. Coplen[145] reviewed more recent experience as of 1997. Coplen[145] indicated prenatal ultrasound distinguishes poorly between hydronephrosis (hopeful) and renal dysplasia (hopeless). Dysplasia is often present by the time severe dilation and oligohydramnios is detected and is irreversible. Prenatal intervention is technically feasible, but the survival rate is only 47% (increase of 6% in a decade), and the complication rate is 45%.

The results of serial observations are applicable only to cases diagnosed by maternal-fetal ultrasonography. There is little debate that certain SFU grade I and probably grade II cases have a favorable outcome with this type of management.[126] The key question in the serial observation is what is the percentage of cases in which there will be progressive ipsilateral renal deterioration during observation. Most of the series with the exception of Koff's[151] have applied the serial observation management strategy to patients with unilateral hydronephrosis and ipsilateral split renal function of greater than 35% or 40%. For the purpose of this review, the results of Ransley and colleagues,[146] Cartwright and associates,[147,148] Duckett,[149] Poulsen and coworkers,[150] and Koff[151] were analyzed. The consensus of results indicates that 15% to 33% had progressive ipsilateral renal deterioration. Koff's series[151] reported the lowest deterioration rate at 7%. The second common reason for delayed operation in the observation group is recurrent febrile urinary tract infection, which occurs in about 3% to 5% of such patients.[152]

In their observation series, Ransley and colleagues[146] reported that after delayed surgery indicated for renal function loss, 36% had complete recovery, 29% had partial recovery, 21% had no change, and 9% had further deterioration. Most series reported that about half of the patients did not regain lost function after pyeloplasty.[126,146,153-157] Again, Koff's series[151] was the exception with 100% recovery. Cartwright and associates[148] confirmed Koff's results.

Results of open pediatric pyeloplasties are often quoted as being the comparable "gold standard" by which all other forms of management are compared. This "gold standard" has no set of criteria of initial inclusion, set follow-up, or even criteria of success. The reoperative rate is very low at 1% in 153 pyeloplasties in the series by Hendren and coworkers,[142] 0% in Duckett's series from Philadelphia,[149] 0.9% in the series by Rushton and colleagues (108 patients),[143] and 4.7% in the series by Woo and Farnsworth (55 infants).[144] In the later series when temporary internal double-J stents were employed, the reoperation rate was 0%. The ultimate favorable outcomes as determined by objectives (radioisotope drainage) were 94% in Woo and Farnsworth (55 infants),[144] 98% in Rushton and colleagues (108 patients),[143] and 100% in Children's Hospital of Philadelphia (70 cases).[149]

The timing of open surgery is also important. King and associates,[158] in determination of results from operating on serious problems in neonates, noted significantly better improvement in children operated within 3 to 16 days of birth compared with older children. Ransley and colleagues[146] showed that pyeloplasty performed at 3 months may be too late. We prefer the work of Dowling and coworkers,[159] who showed (in 41 patients) that repair before 1 year of age permits maximal improvement of renal function. Mayor and coworkers[160] also confirmed these results.

Figenshau and Clayman[129] collectively published the results of endopyelostomies in children. These patients were generally older than the patients in the open series (average age 8.4 years). Different criteria of success were applied, but the average was 86% (82% primary and 92% secondary). These results are summarized in a comprehensive review by these authors. They also summarized the collective experience from balloon dilation. Experience is small, with only 49 total reported procedures, and a rate of success of 63% is clearly less than open procedures.

SELECTION OF INVESTIGATION AND MANAGEMENT IN THE NEW MILLENNIUM

Families of children with pediatric hydronephrosis seeking their own consultation on the Internet encounter a bewildering difference of opinion regarding the type of imaging to be used, criteria for necessity, timing of surgery, and types of surgery to be employed. We council the families in the following manner:

1. There is a tremendous variation in severity and significance of pediatric hydronephrosis.
2. A favorable prognosis is more common than an unfavorable one.
3. The natural history in individual patients varies, and tests are not 100% predictive.
4. In cases with SFU grade I and grade II, no caliectasis and no parenchymal atrophy (on ultrasound or CT urogram), and split renal function greater than 90% (in unilateral cases) are favorable and warrant serial observation, which is usually highly successful.
5. SFU grade IV cases, with demonstrable measurable parenchymal atrophy, split renal function less than 35% (particularly if it deteriorates) and unfavorable provocative renography or pressure flow studies, are unfavorable. These patients are likely to require surgery, and the best results are most likely if surgery is performed in infants younger than 1 year of age.
6. If serial observation is selected, the importance of applying the same techniques performed by the same people in a serial fashion cannot be overstated. The patient's parents and their insurance company (third party) must undertake the responsibility of serial observation.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 21

URETEROVESICAL JUNCTION ANOMALIES: MEGAURETERS

David B. Joseph

The word *megaureter* conveys the image of a grossly dilated ureter, but the term remains nonspecific and, by itself, does not provide insight into the etiology or pathophysiology of the condition or the potential outcome of affected individuals. Knowledge of the megaureter changed greatly during the 1990s owing to fetal ultrasonography. Pediatric urologists are now confronted with a large cohort of children with the diagnosis of an asymptomatic megaureter. This population has allowed us to follow the natural history of the megaureter and to gain better insight into treatment (Fig. 21-1).

HISTORICAL PERSPECTIVE

Megaureter has been synonymous with dilated ureter, megaloureter, wide ureter, big ureter, and hydroureter—all descriptive terms that lack true meaning.[1,2] The normal ureteral diameter in children rarely exceeds 5 mm. This was first reported by Cussen in 1971[3] and later supported by Hellstrom and associates in 1985.[4] Cussen's work[3] was based on autopsy investigation of the urinary system in infants and children. He found that a child's ureter consistently measured less than 5 mm. Hellstrom and associates[4] reviewed excretory urograms in 100 boys and 94 girls. They directly measured ureteral size from the imaging studies and uniformly found the ureter to be less than 6 mm in diameter.

In an attempt to improve communication and refine the understanding and the significance of megaureter, a working party of pediatric urologists was created.[5] They presented their findings and recommendations in 1976 at an international pediatric urologic seminar in Philadelphia. An agreement was made on standardization of nomenclature and classification of the megaureter. The group defined the megaureter as primary when it was a lesion intrinsic to the ureter and as secondary when it was a reaction of the ureter to a process elsewhere. This group created the *ABC classification* of a megaureter: *A* represented a refluxing ureter; *B*, obstructed ureter; and *C*, nonrefluxing, nonobstructed ureter. This classification was reported by Smith and colleagues in 1977.[6] King[7] subsequently modified this classification in 1980 by adding a fourth group that consisted of the refluxing, obstructed megaureter (Fig. 21-2). He maintained the primary and secondary subclassifications. King's classification now is most often referred to when describing a megaureter.

ANATOMY

To understand pathophysiology, it is important to have a framework of normal anatomy. Anatomically, the ureter is divided into three distinct regions: (1) the ureteropelvic junction, (2) the middle spindle, and (3) the ureterovesical junction. The ureterovesical junction is subsequently divided into the juxtavesicoureter and the terminal ureter. The terminal ureter separates into intramural and submucosal segments.[8]

The ureter is enclosed in a loose, ill-defined sheath beneath the peritoneum. This sheath is a protective barrier for the adventitia, particularly when confronted with a neoplastic or inflammatory retroperitoneal process. Proximally, the ureteral sheath and the ureteral adventitia become continuous with the renal pelvis. Distally, the sheath and ureteral adventitia join to form the Waldeyer sheath, which extends into the bladder wall as a portion of the deep trigone.[8]

The ureter lies within the sheath and is composed of three layers: adventitia, a muscular coat, and mucosa. The adventitia consists of longitudinally running collagen fibers.[9] The adventitia along with the outer ureteral sheath is loosely attached to the underlying muscularis, allowing for free peristaltic activity.

The muscularis comprises smooth muscle cells interspersed with collagen fibers. The muscle bundles are arranged in three distinct layers—inner longitudinal, middle circular, and outer longitudinal (Fig. 21-3).[10] This configuration changes into longitudinally oriented muscle fibers with sparse collagen as the ureter enters the bladder and intramural region.[11,12] The mucosa consists of many layers of transitional epithelium lying directly on the lamina propria.

The ureter is supplied by a rich anastomotic network of arteries. The proximal ureter is vascularized predominantly by an artery originating from the renal artery. The aorta and gonadal arteries give off branches for the middle spindle. The distal ureter is supported by arteries from the internal iliac, superior, and inferior vesical arteries.[13] A periureteral arterial plexus courses through the adventitia.

The ureter receives neuronal input via the renal and aortic plexus proximally. Unmyelinated nerves travel throughout the adventitial layer.[9] The middle spindle is innervated by the superior hypogastric plexus and the ureterovesical segment by the pelvic plexus.[14] Schulman[15] identified adrenergic and cholinergic nerves within the ureter. Ureteral peristalsis does not seem to depend on neuronal input, however. Neuronal input may simply have a modulating function on ureteral peristalsis.

PATHOPHYSIOLOGY

Obstructed Megaureter

Using King's description, pathophysiology is dictated by ureteral classification. The primary obstructed megaureter has generated the greatest degree of interest and investigation. Endoscopically, the obstructed ureteral orifice has a normal appearance and inserts appropriately on the trigone. Caulk in 1923[16] and Swenson and associates in 1952[17] equated the obstructed megaureter to that of the enlarged megacolon seen in Hirschsprung disease. This pathophysiology has been refuted, however, on the basis of histologic evidence showing ganglia present in the distal, primarily obstructed megaureter in a distribution similar to that of a normal ureter.[18]

Several different histologic abnormalities have been associated with the primary obstructed megaureter, and these likely reflect a spectrum of pathologic events as its etiology. A localized deficiency of muscle fibers noted within the ureterovesical ureter with hypertrophy of circular muscle bundles immediately proximal to the deficiency has been described as a distinct adynamic distal segment resulting in obstruction.[19,20] In an autopsy series by Tanagho and coworkers,[21] the intramural ureter was composed of circularly oriented fibers instead of the longitudinal fibers normally seen. The degree of obstruction was correlated with the percentage of circular fibers. Gregoir and Debled[22] found three types of obstructed megaureters: those with dense collagen infiltration of the terminal ureter, distal circular muscular hypertrophy, and various degrees of distal muscular dysplasia.

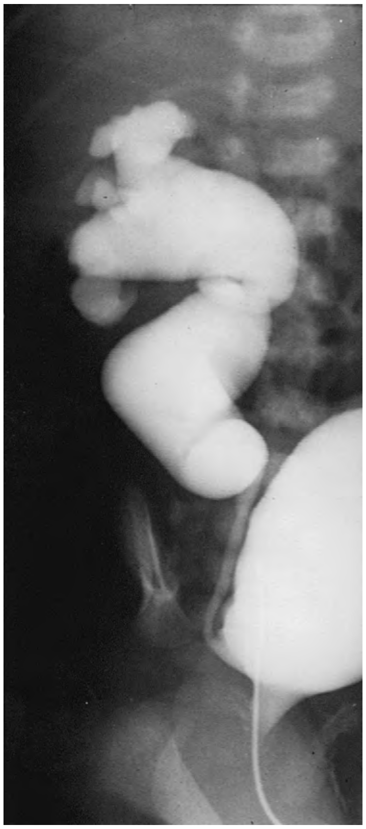


Figure 21-1 Obstructed refluxing megaureter with an unusually long, obstructing distal ureterovesical segment.

Electron microscopy has elucidated further the pathologic process of the obstructed megaureter. Several investigators have identified an increase in collagen deposition between the lamina propria and muscle bundles of the distal ureter.[23-25] These pathologic changes include muscular derangement and increased interstitial connective tissue, which are confined to the ureterovesical junction, sparing the middle spindle and ureteropelvic junction.[26]

Dixon and associates[27] assessed the histologic structure of primary obstructed ectopic ureters. They found the terminal ureter was encircled by an additional thick collar of smooth muscle with normally oriented muscle layers but a diminished diameter. They speculate this embryologic malformation does not resolve spontaneously and may become the subgroup of obstructed megaureter that requires early intervention.

Allowing the megaureter to express its natural history has confirmed that some forms of obstructed megaureter improve with time.[28-33] This spontaneous improvement may be due to segmental maturational development of the distal ureter. Nicotina and associates[28] postulate segmental hypoplasia of the inner longitudinal muscle layer and the possible pathogenic involvement of transforming growth factor-β (TGF-β), which has been shown to affect maturation of smooth muscle cells. TGF-β delays muscle cell differentiation and is detectable in 11- to 21-week-old fetuses, but diminishes thereafter. Nicotina and associates[28] found TGF-β in distal ureters of children who had obstructive uropathy and who were younger than 2 years, but not in children who were older than 2 years and who had been operated on for nonobstructive causes. They postulate that the spontaneous improvement in the obstructed megaureter may correlate with TGF-β depletion within the first 2 years of life.

Gene assessment is beginning to shed light on the underlying pathophysiology of obstructive megaureter. Hohenfellner and associates[34] have shown an increase in angiotensin II type 2 receptors in patients with a primary obstructive megaureter. Further research into gene identification may play a future role in management of the megaureter. Current investigation into the contractile function of the smooth muscle wall of the megaureter and its adrenergic regulation may prove helpful in new options for pharmacotherapy.[34-36]

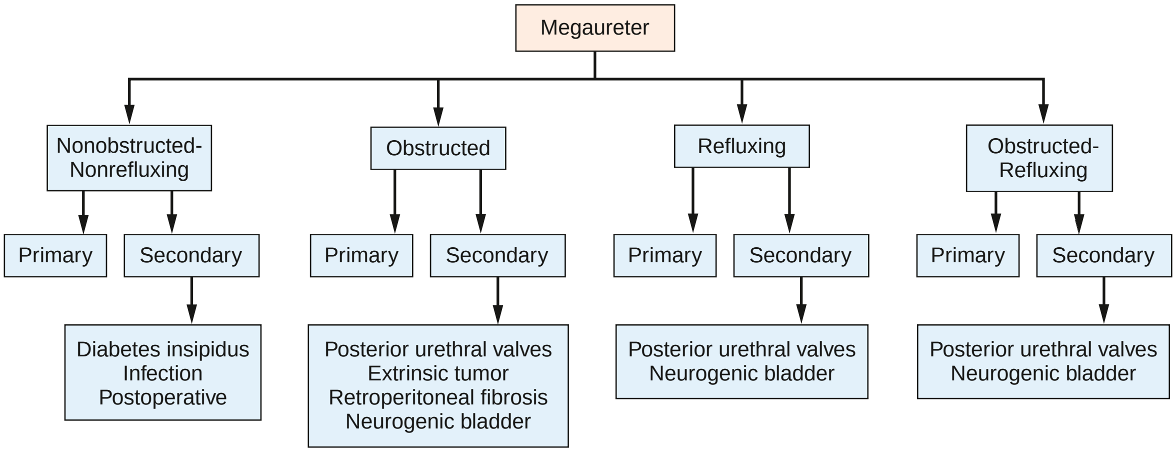

Megaureter
Nonobstructed-Nonrefluxing
Obstructed
Refluxing
Obstructed-Refluxing
Primary
Secondary
Primary
Secondary
Primary
Secondary
Primary
Secondary
Diabetes insipidus
Infection
Postoperative
Posterior urethral valves
Extrinsic tumor
Retroperitoneal fibrosis
Neurogenic bladder
Posterior urethral valves
Neurogenic bladder
Posterior urethral valves
Neurogenic bladder

Figure 21-2 Clinical classification of a megaureter. (Adapted from King LR. Megaloureter: definition, diagnosis and management. *J Urol.* 1980;123:222-223.)

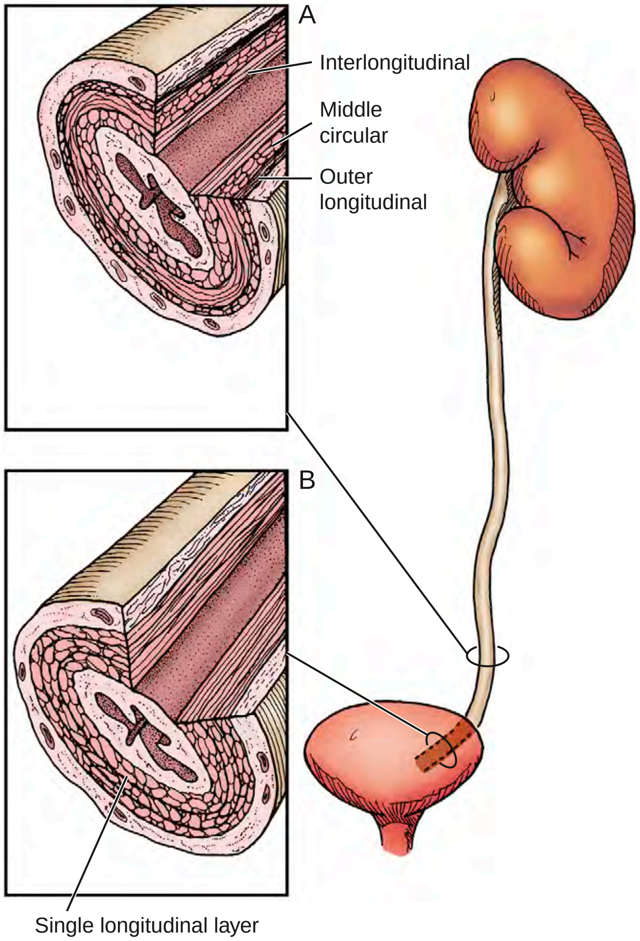


Figure 21-3 Ureteral anatomy. **A,** Cross section of distal ureter shows that the muscularis comprises three layers of smooth muscle bundles—the interlongitudinal, middle circular, and outer longitudinal. **B,** Cross section of the intramural ureter shows only the longitudinally oriented muscle fibers.

Refluxing Megaureter

A refluxing megaureter is endoscopically characterized by a laterally positioned, gaping ureteral orifice. Pressure from bladder filling and cyclical voiding can be transmitted into the ureter, resulting in mechanical enlargement of the ureter (Fig. 21-4). Lee and associates[37] showed that in addition to a lateral position, there are inherent changes in a refluxing megaureter that affect its pathogenic state. They found a twofold increase in the ratio of collagen fibers to smooth muscle fibers in refluxing megaureters compared with those of obstructed megaureters and control ureters.[38] Lee and associates further defined collagen fiber types and showed an increase in collagen types I and III for obstructed and refluxing megaureters. Refluxing megaureters contained a significantly greater percentage of type III collagen, however, than other megaureters. Type III collagen is a less distensible fiber, raising speculation that this intrinsic characteristic results in a stiffer ureter; this may have an important role in the decreased success rate after operative correction of refluxing megaureters compared with the success noted in other forms of megaureters.[37]

Refluxing megaureter associated with prune-belly syndrome (triad of Eagle-Barrett) represents a unique abnormality.[39] The gross appearance of these ureters is elongated, tortuous, and dilated. On endoscopic examination, the ureteral orifices are lateral, look like a "golf hole" in appearance, and are frequently associated with a diverticulum. The distal ureter is often asymmetrically involved, showing significant ectasia (Fig. 21-5). Secondary obstruction may occur with kinking and folding of the redundant ureter. Primary obstruction has been reported at the ureterovesical junction in a select group.[39] Seen microscopically is an increase in fibrous tissue at the expense of normally developed ureteric muscle. Gearhart and coworkers[40] showed that children with triad syndrome and vesicoureteral reflux have an increased ratio of collagen to smooth muscle fibers in the muscularis. This increased fibrous tissue may help explain the poor dynamic characteristics of the ureter, which lead to ineffective peristalsis and urinary stagnation.[39] Ehrlich and Brown[41] reported the degeneration of nonmyelinated Schwann fibers and a decreased number of nerve plexuses, which may contribute to decreased ureteral peristalsis. Ureteric abnormalities tend to predominate in the distal portion of the ureter; this becomes important when considering operative intervention.

DIAGNOSIS

The popularity and routine use of fetal ultrasonography has dramatically increased the diagnosis of megaureter. Brown and colleagues[42] delineated the striking impact that fetal ultrasonography has had on the identification of megaureter. Before the advent of fetal ultrasound, the diagnosis of megaureter was most often made because of clinically significant symptoms, particularly infection, hematuria, and pain.[1] Brown and colleagues[42] showed that in the pre-ultrasonography era, clinically significant megaureters accounted for 8% of children found to have hydroureteronephrosis on imaging studies, preceded by ureteropelvic junction obstruction (22%), posterior urethral valves (19%), and ectopic ureterocele (14%).[42] Fetal ultrasonography has identified a greater presence of megaureter in the general pediatric population. Megaureters are reported to occur in approximately 23% of neonates noted to have antenatal hydroureteronephrosis, now ranking second in the differential diagnosis of neonates with hydronephrosis and surpassed only by ureteropelvic junction obstruction, present in approximately 41%.[42]

Megaureter occurs more often in boys and more often on the left side. Contralateral renal agenesis has been noted in approximately 9%.[1] Given that megaureter is not evolving into a more common pathologic state, this increased incidence can be explained by a more liberal use of fetal ultrasonography and improved technology. An unknown percentage of infants identified to have an asymptomatic megaureter subsequently develop clinical symptoms; this places a greater burden on imaging technology and our ability to assess the true clinical significance of the pathologic state of megaureter.

EVALUATION

Ultrasonography

Ultrasonography is the primary imaging modality used to assess antenatal hydronephrosis and is the initial imaging study obtained for symptomatic genitourinary abnormalities. Ultrasound should have a key role in the assessment of megaureter. Evaluating the size, shape, tortuosity, and bulbar appearance of the ureter in conjunction with similar findings of the renal pelvis can often give the impression of an obstructive process. The ureter can often be traced from the renal pelvis to its distal

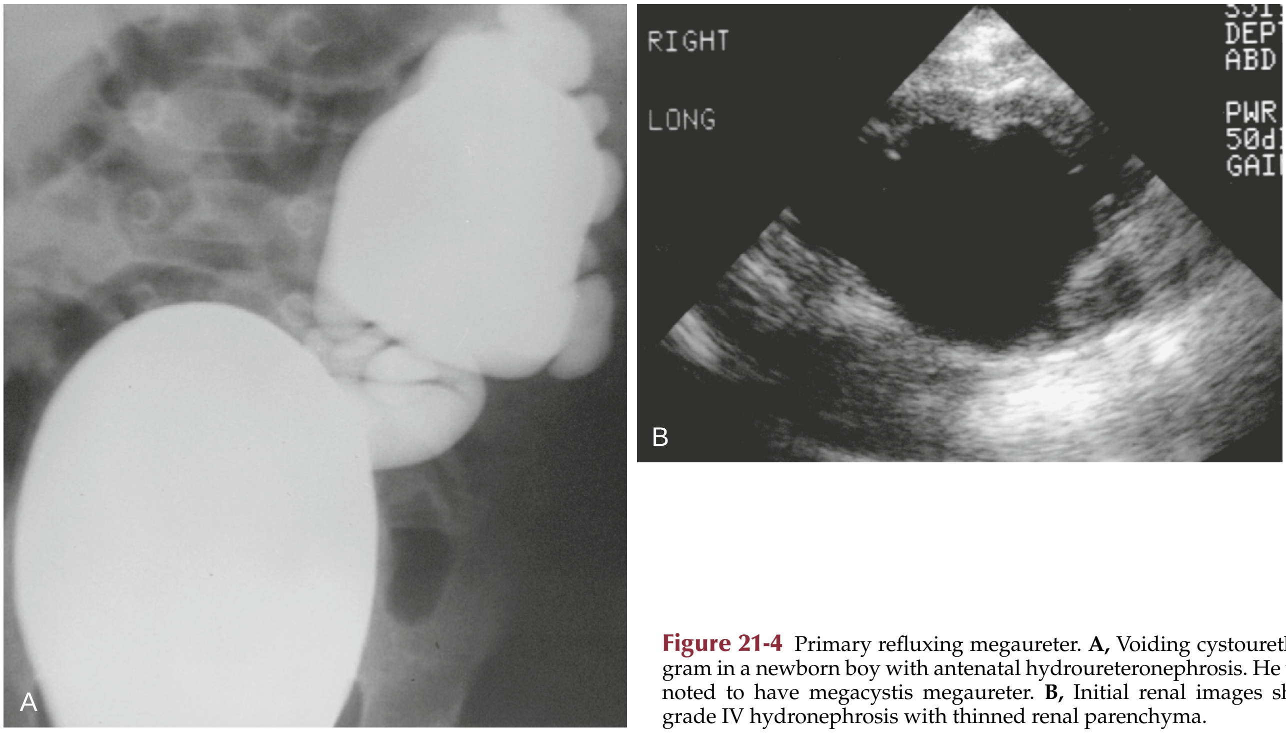


Figure 21-4 Primary refluxing megaureter. **A,** Voiding cystourethrogram in a newborn boy with antenatal hydroureteronephrosis. He was noted to have megacystis megaureter. **B,** Initial renal images show grade IV hydronephrosis with thinned renal parenchyma.

insertion. Careful pelvic ultrasound studies can assist in the differential diagnosis of megaureter. The ureter is often seen to enter an obstructed ureterocele or to be in an ectopic position within the bladder neck or posterior urethra. An obstructed distal segment may be noted when a peristaltic wave of urine stops abruptly a few centimeters proximal to the bladder and rebounds into the dilated proximal ureter. The echogenicity of the kidney is a helpful parameter used to distinguish between an obstructive and nonobstructive process, with increased echogenicity supporting obstruction.[43] Ultrasonography lacks the ability to measure a dynamic process, however, and the true significance of any abnormal megaureter must be determined by a functional imaging study.

Voiding Cystourethrography

Voiding cystourethrography is essential when evaluating the megaureter to rule out vesicoureteral reflux. A conventional fluoroscopic cystogram is preferred over a nuclear cystogram in that the anatomic appearance of the bladder, bladder neck, urethra, and ureters is necessary for precise diagnosis and treatment. The cyclical voiding cystourethrogram is beneficial when an ectopic, sphincteric ureter is suspected. In this scenario, the ureter can be obstructed when the bladder is at rest and refluxing only during the voiding phase. Cyclical evaluation may be required to document the refluxing phase. Blickman and Lebowitz[44] characterize the refluxing obstructed megaureter as having the appearance of a markedly enlarged proximal ureter associated with a normal-appearing ureterovesical segment.

Excretory Urography

Excretory urography is waning as a diagnostic modality in the evaluation of pediatric uropathy. Even with tomography, the information gained is limited. Stool, bowel gas, and immaturity of the neonatal kidney limit its utility. In addition, the degree of hydronephrosis noted does not equate to severity of obstruction. Rarely, excretory uropathy may have a helpful role when further anatomic definition is required.[45] When anatomic detail is required, furosemide (1 mg/kg) given 3 minutes before contrast material enhances the multislice CT scan and shows promise at defining the pathologic defect better than intravenous urography and ultrasonography.[46]

Renography

Diuresis renal scintigraphy provides the greatest quantitative information of functional and dynamic data. With the assessment of several parameters, including renal uptake, excretion, time to peak activity, and time to half peak after furosemide washout, the degree of obstruction can be assessed. Two common radiotracers used to evaluate obstruction in pediatrics are technetium 99m diethylenetriamine penta-acetic acid (Tc^{99m} DTPA) and technetium 99m mercaptoacetyltriglycine (Tc^{99m} MAG3).[47,48] DTPA is a glomerular agent and has been discouraged from use during the first month of life because of low neonatal glomerular filtration rates. MAG3 is extracted by the kidneys and is dependent on effective renal plasma flow, not glomerular filtration rate. This makes MAG3 a more attractive agent, especially during the neonatal period.[47] MAG3 also provides better interpretation of function with less background artifact.

Many variables can have a role in data acquisition and interpretation. For that reason, renal scintigraphy must be performed in a standardized manner using a protocol that optimizes hydration, administration of diuretic, and acquisition of time-activity curves.[49] When assessing the megaureter for an obstructive pattern, it is important to have two sets of activity curves—one over the kidney and the other over the ureter. Isolating simply over the kidney could produce deceiving results showing an acceptable washout of the radiotracer

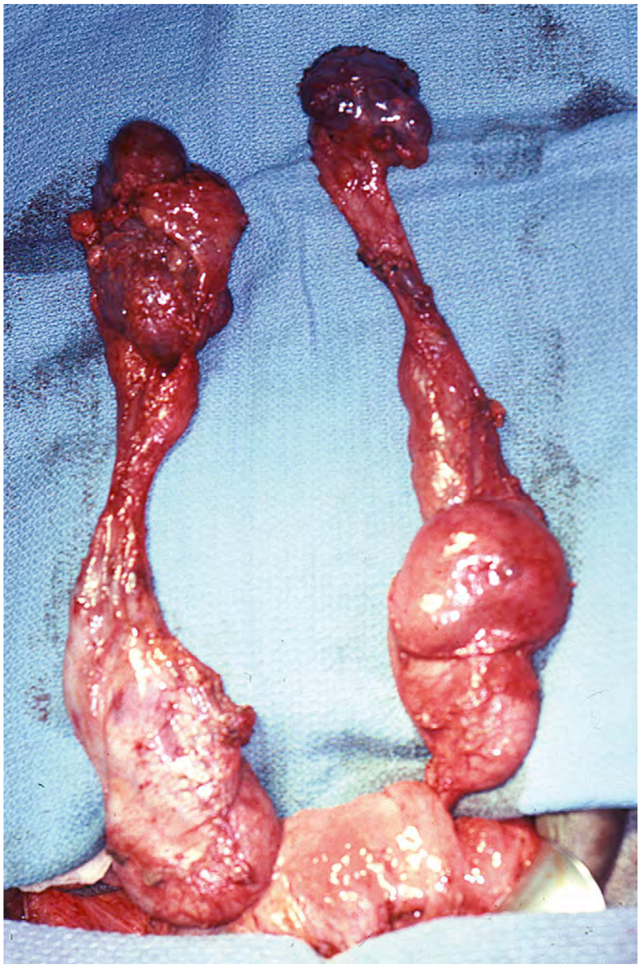


Figure 21-5 Gross appearance of the ureter in prune-belly syndrome. These ureters are elongated, tortuous, and dilated. There is often ureteral asymmetry with the distal ureter showing significant ectasia. (From Joseph DB. Triad syndrome and other disorders of abnormal detrusor development. In: Gonzales ET, Bauer SB, eds. *Pediatric Urology Practice.* Philadelphia: Lippincott Williams & Wilkins; 1999.)

from the kidney only to be washed into an obstructed ureter (Fig. 21-6). Obtaining a second set of curves over the ureter when renal washout is noted helps confirm distal ureteral obstruction. Half-time clearance less then 10 minutes seems to be predictive of a nonobstructive process; however, half-time greater than 20 minutes does not confirm obstruction. Technetium 99m dimercaptosuccinic acid (Tc^{99m} DMSA) is particularly useful in assessing renal parenchymal changes owing to scarring. DMSA also may become a better predictor for estimating the potential of functional recovery after surgery for obstruction.[50,51]

Magnetic Resonance Urography

Magnetic resonance urography (MRU) has the capability of providing greater insight into anatomic abnormalities, particularly related to the ectopic insertion of the distal ureter into the bladder neck or vagina. Gadolinium-enhanced MRU is especially beneficial in patients with renal insufficiency and patients allergic to iodinated contrast media.[52,53] The need for oral or intravenous sedation in young patients and the increased expense currently limit the use of MRU.

Percutaneous Perfusion Studies

Upper urinary tract urodynamic assessment can be obtained in difficult cases to help assess distal ureteral obstruction. The Whitaker test traditionally has been the procedure of choice.[54] The Whitaker test has significant limitations in pediatric patients, however. First, it is invasive, requiring percutaneous placement of a renal catheter and bladder catheterization, and may necessitate mild sedation or general anesthesia. Second, Whitaker[54] described this procedure using a constant infusion of 10 mL/min, with obstruction defined as an elevation in renal pressure greater than 22 cm H_2O. Few data define the appropriate rate of infusion that can be safely accommodated by a normal infant ureter. Infusing the renal pelvis of an infant or child at a rate of 10 mL/min may overcome the peristaltic flow potential of the normal ureter. A more appropriate technique may be to perform a constant perfusion test, which allows for recording of renal pelvic pressure, while maintaining a continuous variable infusion of testing medium at a specified pressure.[55,56]

Fung and associates[56] explored ureteral opening pressure as a novel parameter for evaluating the obstructive nature of pediatric hydroureteronephrosis. Renal pelvic pressure was assessed while documenting the passage of contrast material from the distal ureter into the bladder. The infusion rate was calculated individually for each patient and was maintained within a physiologically relevant range. A pressure increase of 14 cm H_2O within the renal pelvis was deemed consistent with distal ureteral obstruction. Although this approach for identifying ureteral obstruction remains invasive, it eliminates the problems of the infusion rate noted in the classic Whitaker study.[56]

DIFFERENTIAL TREATMENT

Therapeutic intervention of the megaureter depends on accurate classification. Secondary causes of a megaureter justify treatment of the primary problem whether it is due to a neurogenic bladder, posterior urethral valves, ureterocele, diabetes insipidus, or a retroperitoneal process. Specific treatments for these problems are described elsewhere.

Refluxing Megaureter

Grades IV/V and V/V vesicoureteral reflux (according to International Study Classification) traditionally has prompted operative intervention.[57] For older children presenting with symptomatic urinary tract infections, this approach may be appropriate. Growing experience shows, however, that operative intervention is not required as initial management in neonates with refluxing megaureters, especially when identified during the workup of antenatal hydronephrosis. High-grade vesicoureteral reflux in neonates occurs more often in boys than girls. Improvement during the first year of life can be anticipated in many of these children.[57] There is little reason to proceed with intervention in these early years, particularly when an infant has remained symptom-free on prophylactic medical management. Resolution of high-grade vesicoureteral reflux in neonates is not unusual.

Williams[58] first described the constellation of megacystis-megaureter in 1954. Megacystis-megaureter is an association and not a syndrome because underlying pathophysiology is well understood.[59] By definition, the term *megacystis-megaureter*

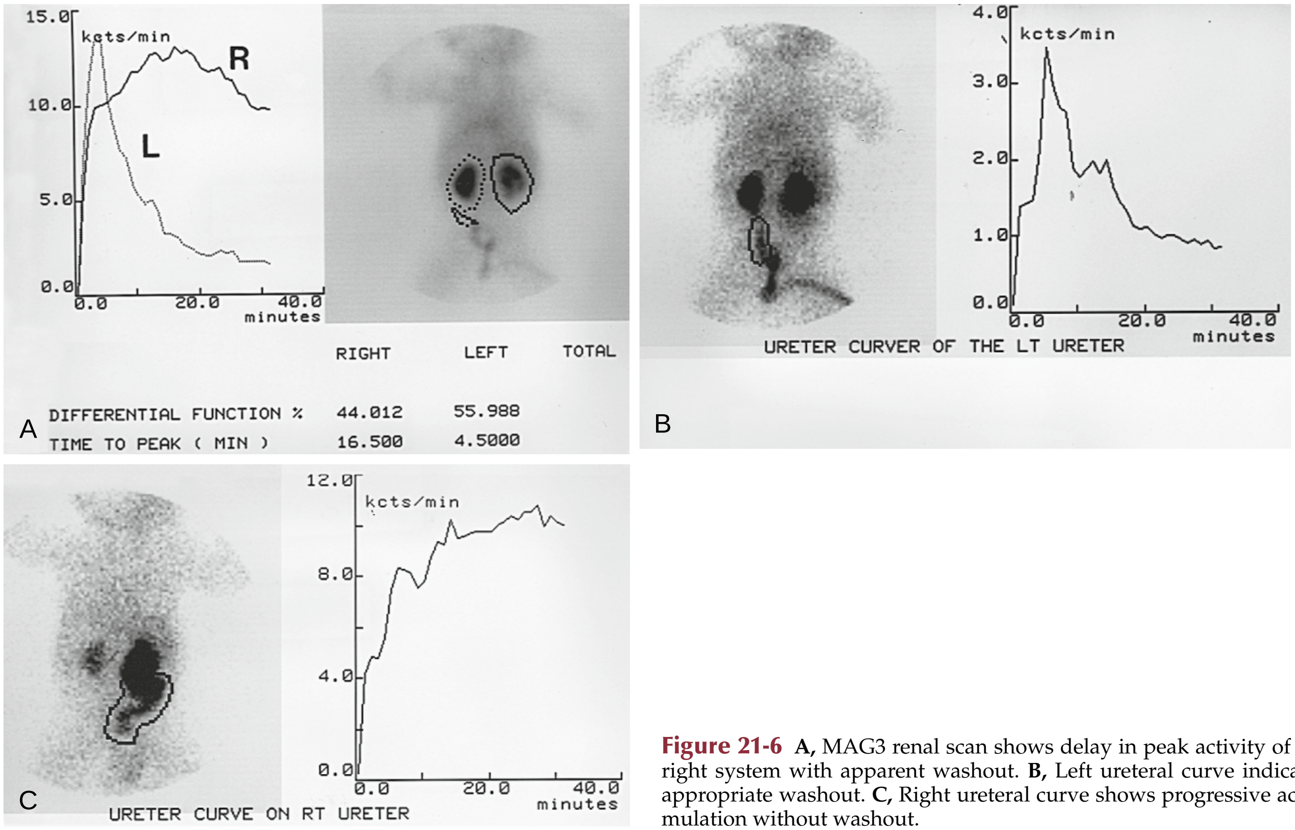


Figure 21-6 **A,** MAG3 renal scan shows delay in peak activity of the right system with apparent washout. **B,** Left ureteral curve indicates appropriate washout. **C,** Right ureteral curve shows progressive accumulation without washout.

should be applied to a large-capacity, thin-walled bladder with massive primary vesicoureteral reflux.[58,59] Megacystis-megaureter occurs in approximately 80% of boys diagnosed antenatally with bilateral reflux and renal impairment.[60] The cause of the male predominance is unknown. There does not seem to be any degree of bladder outlet obstruction. Speculation has been given simply to higher neonatal voiding pressure in boys. Children with megacystis-megaureter show progressive upper tract hydroureteronephrosis and bladder enlargement resulting from the recurrent cycling of urine into the upper tract during a detrusor contraction followed by rapid refilling of the bladder on relaxation of the detrusor after voiding. Over time, this cyclical event leads to increased bladder volume and subsequently increased hydroureteronephrosis.

In children who are toilet trained, double voiding combined with prophylactic antibiotics may be an effective temporizing treatment option. Ten to 15 minutes after the initial void, the child is encouraged to void again, allowing for an overall decrease in volume of retained urine. Positive effects of this technique can be seen first with stabilization of bladder volume followed by reduction in bladder size and improvement of hydroureteronephrosis. In neonates and toddlers who are not toilet trained, intermittent bladder catheterization can be an effective technique to eliminate residual urine, allowing the child to reach an age at which operative correction would be deemed beneficial. Ultimately, children with a megacystis-megaureter are best served by operative reconstruction.[59]

Nonobstructed, Nonrefluxing Megaureter

The advent of fetal ultrasonography and identification of megaureter has disclosed a large percentage of children with a nonobstructing, nonrefluxing megaureter. Ultrasound and static images from urography can show impressive ureteral dilation. A functional study is needed to confirm adequate ureteral drainage. These children benefit from initial medical management centered on prophylactic antibiotics for the prevention of urinary tract infections. Children with a nonobstructed, nonrefluxing megaureter maintain normal renal function, and over time their hydroureter can revert to normal. This subclass of megaureter occurs in approximately 6% to 10% of infants with antenatal hydronephrosis.[61-66] McLellan and associates[67] report 72% resolution of nonobstructed, nonrefluxing megaureter. In their series, grade I resolved within 13 months of age; grade II, within 24 months; and grade III, within 35 months. When grades IV and V resolved, it occurred at a median age of 49 months.

Obstructed, Refluxing Megaureter

Obstructed, refluxing megaureter occurs as a result of a laterally positioned aperistaltic distal segment, or ectopic insertion of the ureter into the bladder neck/posterior urethra. Although not emergent, operative correction of this entity is required to diminish the risk of upper urinary tract deterioration and to reduce risks of urinary tract infections, particularly infections associated with the obstruction component.

Obstructed Megaureter

Before the advent of fetal ultrasonography, the treatment of the obstructed megaureter was straightforward. A child would present symptomatically with a urinary tract infection, abdominal pain, or nausea and vomiting.[1] Adults also present symptomatically and usually require aggressive management.[68] This form of selection eliminated the guesswork currently required to determine which children would benefit from correction of an obstructed megaureter. Children with symptomatic problems have become the numerator in a fraction in which the denominator is unknown. As fetal ultrasound has become routine, it is now obvious that the denominator of children with an obstructed megaureter is substantial; given that this is not related to evolution, it must be presumed that a significant percentage of obstructed megaureters do not become clinically significant.

Controversy surrounds the current management of obstructed megaureter.[29,69-72] Medical management based on prophylactic antibiotics has been shown to provide an opportunity for spontaneous regression of megaureter without a compromise in renal function. This situation has placed the burden of when to intervene squarely on the shoulders of the pediatric urologist. Surgical repair of megaureter in an infant is technically possible, but remains a significant challenge even in established pediatric centers. Peters and associates[73] reported a 10% need for secondary operative procedures when correcting an obstructed megaureter in infants younger than 8 months. Many pediatric urologists now believe it is appropriate to temper the initial urge to intervene operatively for megaureter until the child is older than 12 months, at which time technical hurdles do not seem to be as great.[74]

Occasionally, an infant presents with substantial renal compromise secondary to an obstructed megaureter. In this situation, strong consideration should be given to a temporizing distal cutaneous ureterostomy, particularly when the infant is younger than 12 months.[61] A distal ureterostomy adequately drains the upper urinary tract, decreasing the risks of infection and further renal demise. It has been speculated that cutaneous ureterostomy allows the decompressed ureter the opportunity to regain tone and a more normal caliber as the child grows and develops.[61]

OPERATIVE APPROACH

Temporary Diversion

Temporary urinary diversion may have benefits as indicated earlier. A practical approach for a severely obstructed unilateral megaureter is to proceed with distal cutaneous ureterostomy. This technique is rapid, has minimal morbidity, and can often be performed in an outpatient setting. With a child in the supine position, the ureter is approached from a 2-cm incision placed within an ipsilateral low inguinal skin crease. A muscle-splitting exposure is used to enter the space of Retzius. It is helpful to have the bladder half full to facilitate the dissection. Dissection is continued laterally and superiorly, mobilizing the peritoneum from the bladder. In most situations, the ureter is easily visualized because of its size. A cautious approach should be taken before transection because bowel can be confused with a distended ureter, particularly in an infant. If there is any doubt about the structure that has been mobilized, a 21-gauge needle should be passed, aspirating the contents to confirm urine. If the ureter is not easily identified, the obliterated umbilical artery provides a suitable landmark for initiating the search.

The obliterated umbilical artery should be transected in the deep pelvis adjacent to the bladder, and the ureter is found just beneath that point. The ureter is mobilized, and the decision whether to fashion an end or a loop cutaneous ureterostomy is made. The ureter should be secured to the anterior rectus fascia with 4-0 or 5-0 absorbable suture and to the skin with the same. The size of the ureter prevents postoperative stenosis. Lee and associates[75] report a unique form of internal temporary diversion. They create a refluxing anastomosis securing the side of ureter proximal to the obstruction to the dome of the bladder. This anastomosis allows for ureteral and renal decompression as the child matures and waits for definitive intervention.

Definitive Reconstruction

When definitive urinary reconstruction is necessary, the initial approach to the ureter can be intravesical, extravesical, or combined. The dilated ureter is often exceedingly redundant and tortuous. Straightening the ureter is required without devascularization. The functional capability of the ureter to transmit urine into the bladder through peristalsis parallels the degree of the hydroureter. Ureteral tapering should enhance urinary flow into the bladder. The ureter also must be tapered to achieve a ureteral diameter that allows for a 4:1 to 5:1 ratio of tunnel length to ureteral diameter necessary for an antirefluxing repair. Enough ureter should be mobilized to taper the intravesical ureter and a short portion of extravesical ureter. There should be a gradual transition from the tapered to dilated ureter to prevent a sharp gradient that can act as a pseudo-obstruction. Several tailoring techniques exist for ureteral tapering, including ureteral imbrication and formal ureteral excision.[76-79]

Imbrication

Ureteral imbrication is appropriate for marginally dilated ureters. Two common imbricating techniques include the Starr and Kalicinski plications.[76,77] In the Starr plication,[76] a Lembert suture technique with 6-0 absorbable suture is used to “fold in” the redundant ureter over a 10F or 12F catheter (Fig. 21-7). Kalicinski and colleagues[77] established a plication technique that excludes the redundant ureter from the urinary system (Fig. 21-8). Also, using a 10F or 12F catheter template, the excess ureter is isolated along its least vascular portion. A running 5-0 or 6-0 absorbable suture is passed parallel to the course of the ureter, separating it from the redundant segment. The redundant segment is then folded over the outside of the ureter and secured with a second absorbable suture layer. Using either imbrication technique, the plicated ureter

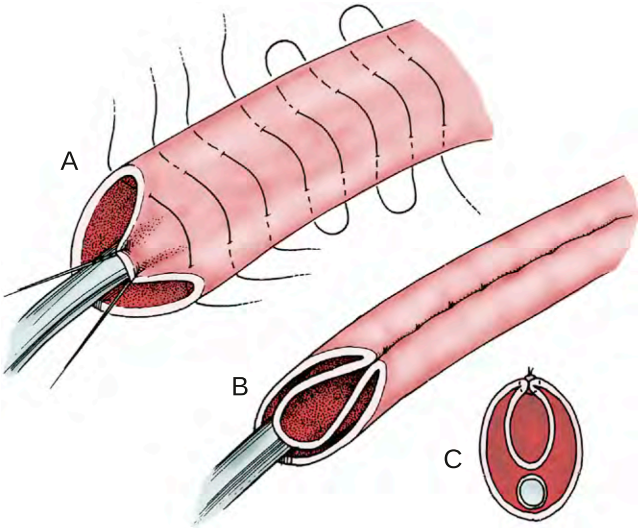


Figure 21-7 **A-C,** Starr technique of ureteral imbrication. The ureter is folded in using a 10F or 12F catheter as a guide. The distal portion is secured with interrupted sutures.

is brought into the bladder and can be secured to the floor in either a cross-trigonal or a Politano-Leadbetter fashion.

The advantage of plication techniques relates to preservation of ureteral blood supply, decreased incidence of devascularization, and minimal risk of urinary leak and obstruction. Ureteral stents may be placed for 3 to 7 days, but are often unnecessary. When massive ureteral dilation is present, imbrication adds unwanted bulk that makes it difficult for the ureter to be accommodated, particularly if a bilateral procedure is performed.

Excisional Tapering

Formal excisional tapering of the ureter is beneficial, particularly when encountering extremely bulky ureters or a bilateral process. Hendren[78] pioneered the technique that has stood the test of time. The ureter is tapered loosely over a 10F or 12F catheter, depending on the child's age and size. Straight Allis clamps are placed longitudinally along the ureter in the region of least vascularity. Angled Allis clamps are placed over the ureter, securing the internal 10F to 12F catheter (Fig. 21-9). Care should be used to prevent the temptation of excluding too much redundant ureter, which results in excessive tapering around the catheter. The ureter is closed in a two-layer technique, first with a running locking 5-0 or 6-0 absorbable suture that directly opposes the mucosa and the muscularis of the ureter. The locking suture technique prevents excessive ureteral reefing. A second running adventitial layer of absorbable suture is then placed. Both running layers are discontinued a few centimeters from the distal end of the ureter. The very distal portion of the ureter is closed with interrupted sutures; this allows for excision of the distal ureter if required without interruption of the running suture line.

The ureter should be stented for 5 to 10 days. Excisional tapering can jeopardize ureteral vascularity. Ossandon and colleagues[80] modified the traditional tapering procedure by opening the ureter and creating two parallel longitudinal incisions through the epithelium and into the muscularis, leaving the adventitia intact. The lateral epithelial strips are removed, and the inner layer is closed in a running fashion. The lateral adventitia is reinforced over the inner closure, decreasing the risk of urinary extravasation.

In most situations, only the portion of the distal ureter that is going to be placed within the bladder and 1 or 2 cm beyond needs to be tapered. There should be a gentle transition from the ureteral hiatus at the bladder to the nontapered ureter. Proximal ureteral tapering is rarely required and is limited to children with persisting proximal hydroureteronephrosis, with an obstructed pattern in the presence of a patent distal ureter.[79] In complex reconstructive cases with large bilateral

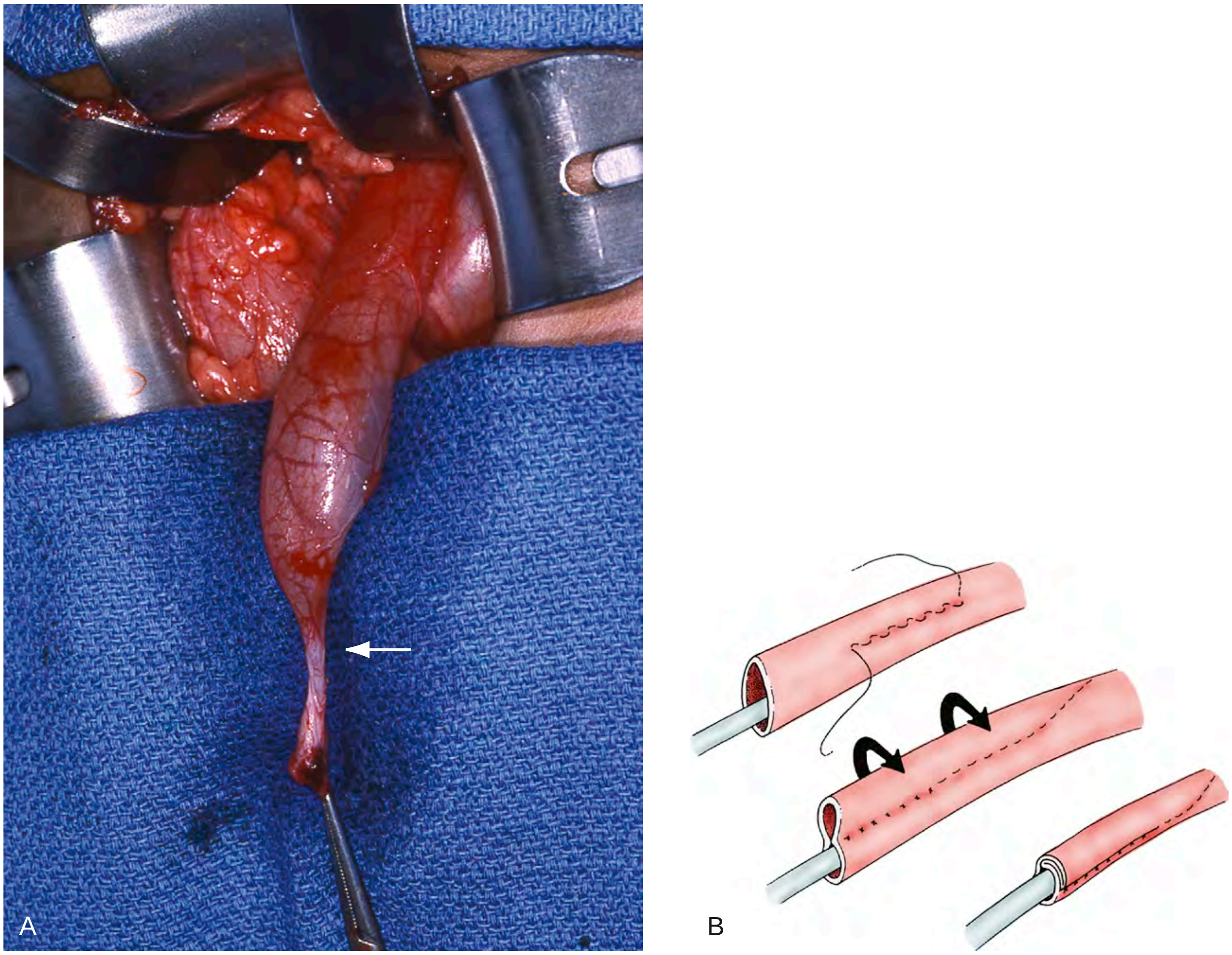


Figure 21-8 **A,** Primary obstructed megaureter secondary to aperistaltic distal segment *(arrow)*. **B,** The Kalicinski technique of ureteral imbrication. The excess segment of ureter is excluded from the flow of urine. It is folded over the ureter using a 10F or 12F catheter as a guide *(arrows)*.

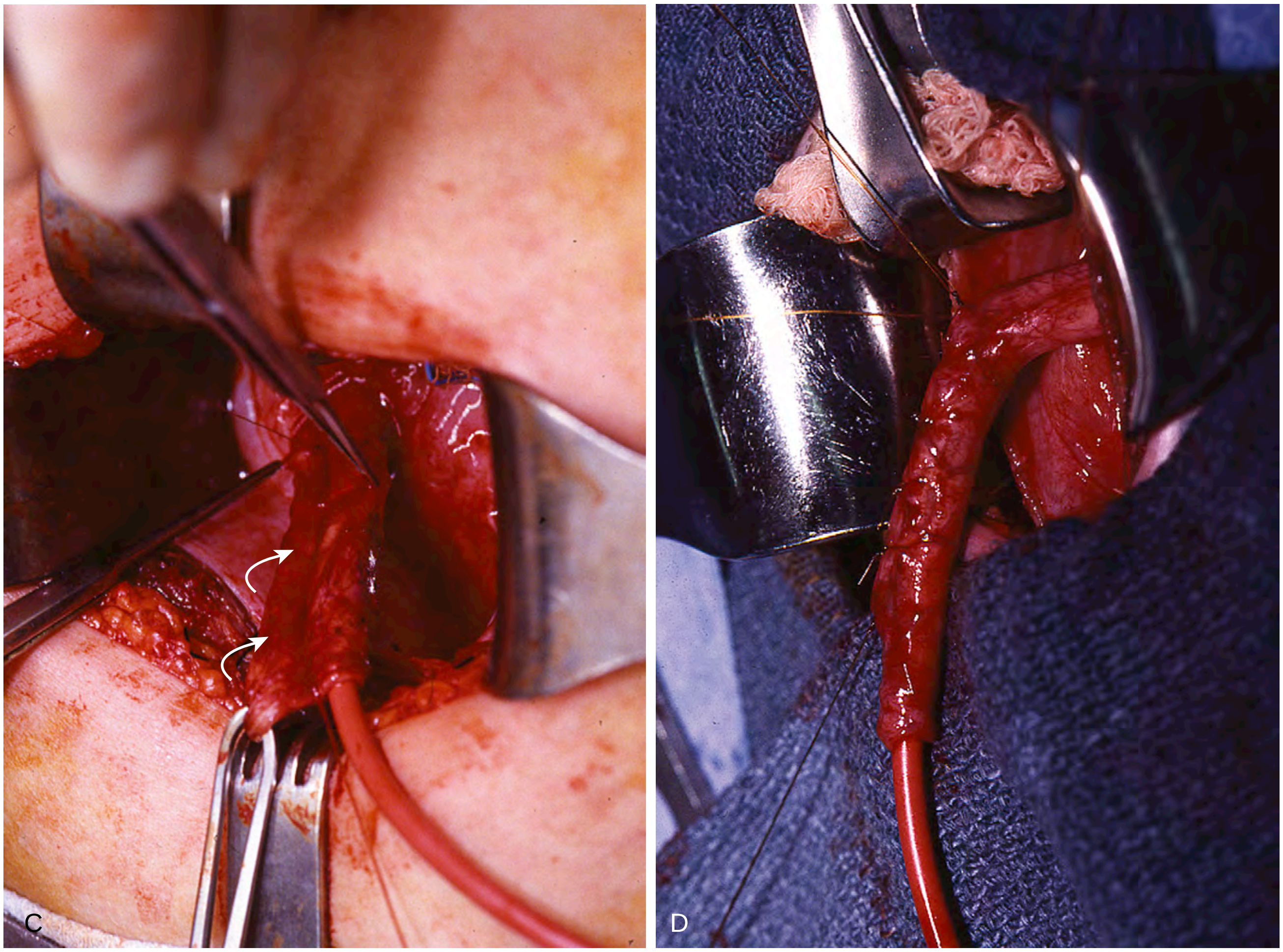


Figure 21-8, cont'd **C,** Kalicinski plication technique isolating the redundant ureter from the distal flow of urine *(arrows)*. **D,** The excluded segment has been folded and secured to the distal ureter.

megaureters, consideration should be given to a transureteroureterostomy and a unilateral tapered reimplant.

POSTOPERATIVE MANAGEMENT

In the immediate postoperative period, children should be maintained on appropriate pain control medications and antibiotics. A full course of antibiotics continues while the ureteral stent is in place. After all stents and drains are removed, antibiotics are changed to a prophylactic dose until obstruction and persisting vesicoureteral reflux have been ruled out. Ureteral stents are not necessary in all tapered ureters; however, initial benefits include decreased urinary extravasation and a scaffold for the ureter to conform to in the postoperative period. This helps prevent kinking, which can occur in the redundant and dilated ureter. The ureteral stent also bypasses the tapered region, which initially may act as an obstruction because of postoperative edema. The need for a Penrose drain varies, depending on the technique used for ureteral tailoring and the presence of an indwelling ureteral catheter. A Penrose drain may be helpful when a ureteral catheter has not been placed, and a substantial portion of tapered distal ureter remains extravesical. When a ureteral stent has been placed, the addition of a Penrose drain is unnecessary. The ureteral stent allows for direct drainage of urine from the involved ureter and acts as a conduit for any extravasated urine.

Ureteral stent removal varies, depending on the procedure performed. With ureteral imbrication, stent removal can occur 3 to 7 days postoperatively. With formal tapering, stent removal is undertaken 5 to 10 days after repair. Ureterograms at the time of stent removal are not beneficial. The combination of postoperative edema and the stent may limit the drainage phase of the ureterogram, giving the appearance of a high-grade obstruction when removal of the stent is all that is required. Before removing the stent, it is advisable to administer a broad-spectrum antibiotic to decrease the likelihood of obstructive urosepsis, which can occur after stent removal even in a child receiving prophylactic antibiotics.

Postoperative ureteral edema persists for 4 to 5 weeks after operative intervention. For that reason, postoperative imaging studies with either ultrasonography or renal scintigraphy are advised at 6 weeks after repair. The initial images on ultrasound may show increased hydronephrosis and proximal hydroureter compared with preoperative ultrasound studies, particularly when repairing a refluxing megaureter. This is often because of the highly compliant proximal ureter and relative resistance to flow through the tapered ureter. Before diagnosing high-grade obstruction, it is important to assess the ultrasound images

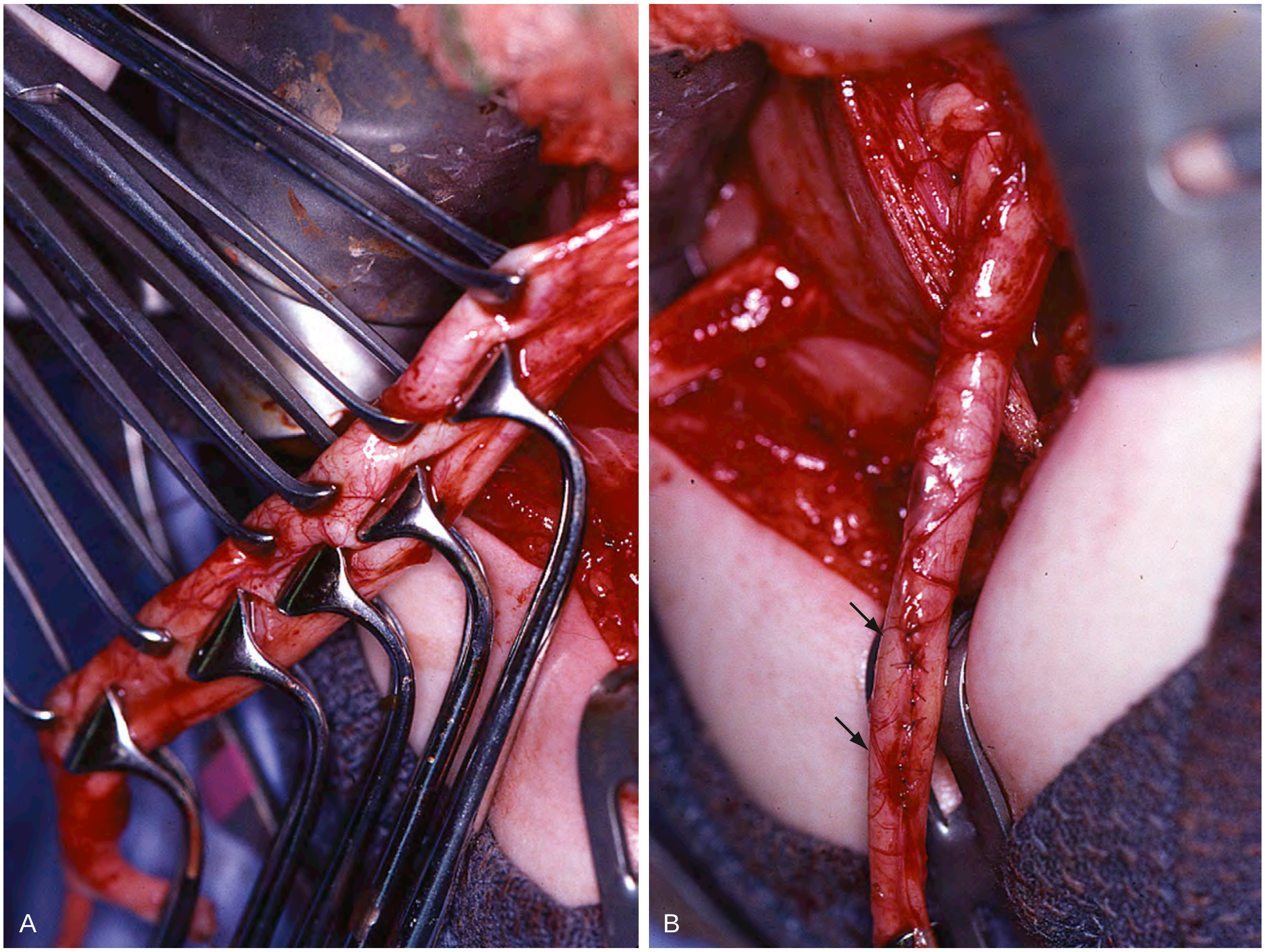


Figure 21-9 **A,** Angled Hendren clamps are placed loosely over a 10F or 12F catheter, securing the retained portion of the distal ureter. Straight Allis clamps isolate the segment to be excised. **B,** Two-layer technique is used to close the ureter, interrupting the distalmost portion and allowing for excision as needed. *Arrows* indicate interrupted portion.

in relation to the preoperative cystogram. Renal scintigraphy is a more effective diagnostic tool for assessing postoperative obstruction and may be required in troublesome cases.

A voiding cystourethrogram is performed approximately 6 months postoperatively to confirm the absence of vesicoureteral reflux. When this state has been reached, prophylactic antibiotics can be discontinued.

COMPLICATIONS

Successful operative outcome in the treatment of megaureter is customary when the operation is performed at pediatric institutions by appropriately trained surgeons experienced in the care of children.[73] Although success can be anticipated when performing a tapered reimplant, the potential complication rate and morbidity are greater than when performing a nontapered ureteroneocystostomy. The two most likely complications include obstruction and persisting reflux. Success rates for ureteral imbrication have been reported to be 93% to 95%,[77,81-83] and success rates after excisional tapering are 74% to 90%.[73,81,83-92]

Postoperative complications may not simply be due to technical error. Inherent ureteral characteristics and bladder dysfunction affect a successful outcome. Increased collagen deposition and altered smooth muscle ratios, seen more often in a refluxing ureter, may be the cause of a higher rate of persisting vesicoureteral reflux after repair of this classification of megaureter.[27,37] Contralateral reflux occurs in children undergoing unilateral megaureter repair for vesicoureteral reflux without correlation to the surgical approach.[65] Caione and associates[93] report that this does not occur when unilateral reimplantation is undertaken for an obstructive megaureter. Their results suggest that the functional anatomy of the trigone is preserved in the congenital obstructive megaureter and altered in the refluxing megaureter.

Postoperative edema after stent removal can lead to true obstruction requiring temporary antegrade diversion. Physician patience is the most prudent course of action to take after antegrade diversion has been obtained to allow for temporary operative edema to subside. This edema may take 2 to 3 months to resolve. Ureteral ischemia does not improve, however, and ultimately requires revision.

Persisting vesicoureteral reflux has been reported to occur in 5% to 45% of tapered reimplants.[73,77,81-87,94,95] Transient mild reflux noted at 6 months can resolve with further time. Reflux persisting longer than 3 years is unlikely to resolve.[73] When significant persisting vesicoureteral reflux occurs, and secondary corrective intervention is required, a formal reoperative procedure is undertaken, with attention paid to preservation of ureteral blood supply and an attempt at maximizing the ratio of ureteral tunneling to a diameter of at least 5:1. In situ ureteral tailoring is an appealing alternative to a formal excisional repair. It achieves a gradual decrease in intraluminal diameter without compromising vascularity and avoids the difficult ureteral dissection. This approach should be considered in cases in which the ureteral tunnel length had been maximized at the first encounter.[94]

CONCLUSION

An asymptomatic megaureter is more commonly encountered as a result of the routine use of fetal ultrasonography. The natural history of megaureter is now unfolding with observation and nonoperative management of many infants. When operative management is required, precise classification of the megaureter, along with intervention directed by a pediatric specialist, can result in a successful outcome.

REFERENCES

For complete list of references log onto www.expertconsult.com

SECTION 2

REFLUX AND ALL OTHER URETERAL ABNORMALITIES

CHAPTER 22

VESICOURETERAL REFLUX: PATHOPHYSIOLOGY AND EXPERIMENTAL STUDIES

Margaret L. Godley and Philip G. Ransley

Vesicoureteral reflux (VUR) is a dynamic event—the retrograde flow of bladder urine into the upper tracts. It occurs normally in the young of many animal species, but is considered abnormal in humans, a feature of disordered anatomy and function at the ureterovesical junction (UVJ). In clinical practice, the term *vesicoureteral reflux* describes a common primary disorder of childhood associated with urinary infection and renal scarring, or "reflux nephropathy." Although the reflux event usually disappears during growth, the disorder is of clinical concern because of the morbidity from ascending urinary infection and the associated nephropathy that can lead to hypertension and renal function insufficiency.

Clinical and experimental studies have been directed at isolating the causal relationships between the pathophysiologic components of the VUR disorder: the reflux event, the urinary infection, and the associated nephropathy. Nevertheless, some of the issues surrounding these associations remain contentious. The VUR disorder overall is not so simple; it cannot be explained by a simple organic abnormality. It is a heterogeneous condition with diverse features, suggesting that compound factors may operate in the genesis of the reflux and its relationships with urinary infection and nephropathy.

Most clinical studies have concerned older children with acquired renal scarring. Experimental studies have been directed at the pathophysiologic effects of the reflux event after birth and the mechanisms for the acquired nephropathy. It is now clear that the contribution of congenital nephropathy in association with VUR has been underestimated. Nevertheless, most children presenting in clinical practice do so after urinary infection, and half already have renal scarring. Most of them are girls, and data from those identified in infancy suggest that most had normal kidneys at birth.

This chapter considers the clinical disorder, the genesis of VUR, and the pathophysiologic interrelationships. The roles of urinary infection and lower tract function are questioned. Clinical management issues are not addressed. The aim is to provide a broad understanding and to stimulate curiosity and activity in evidence-based investigation of the outstanding anomalies that surround this complex disorder.

VESICOURETERAL REFLUX: THE ANOMALY

The assumption that VUR is abnormal is based on the examination of autopsy specimens, speculatively attributed to Galen in 150 A.D.[1] That VUR can occur in humans was first documented in 1893, when Pozzi noted the efflux of urine from the distal segment of a ureter accidentally severed during pelvic surgery.[2] Subsequently, the identification of VUR in humans depended on the development of contrast radiography.

Prevalence

The number of children with VUR at any one time is difficult to ascertain, and the prevalence rate depends on the population sampled. The early studies of small numbers of newborn and premature infants did not show any VUR.[3,4] Bailey[5] in 1979 estimated a prevalence of 0.4% to 1.8% in the general pediatric population. A more recent meta-analysis of reviewed publications suggests the prevalence may be 9% in healthy normal children.[6] This larger percentage can be explained by several factors. The data are heavily skewed by the inclusion of a publication reporting an atypical 30% incidence.[7] That study comprised infants and children who were hospitalized for various conditions, some of which are now known to be associated with urinary tract abnormalities. Repeat micturating cystography in the reflux-positive children on the following day did not show reflux in most children. It is well known that rapid filling of the neonatal and infant bladder can generate a flicker of transient reflux that is not sustained. There is no good evidence for a generally accepted prevalence rate of VUR that is greater than 1% to 2%.

Investigation of 1005 infants with a prenatal renal pelvis dilation greater than or equal to 4 mm identified VUR in 6.9% (equal numbers of boys and girls), an incidence of 0.44% of the population screened by prenatal ultrasound.[8] In infants investigated after an established and specific diagnosis of prenatal hydronephrosis, the incidence increases to 15% to 25%, which reflects a prevalence rate of 0.02% to 0.2% of all live births.[9] Prenatal screening identifies only a few of all children who present with VUR at some stage.

Investigations after clinical presentation with urinary infection show reflux present in 30% to 50% depending on age and gender.[10-15] A survey of 1460 neonates for bacteriuria indicated that VUR and urinary infection may affect only 0.6% of asymptomatic neonates, however.[16] Prevalence rates relate predominantly to the white population. VUR is rare among North African black children presenting with urinary infection or after a diagnosis of prenatal hydronephrosis.[17,18]

The true incidence of reflux at birth most likely is the same in boys and girls, although their clinical problems are different. The lower the thresholds for postnatal investigation,

Table 22-1 **Proportions of Males and Females with Vesicoureteral Reflux Diagnosed after Urinary Infection**

Age (yr)	Series	No.	Males	Females	M:F
Infants (<1)	Rolleston et al (1970)[27]	175	91	85	1.1:1
	Bourchier et al (1984)[28]	36	20	16	1.3:1
	Merguerian et al (1999)[23]*†	128	79	49	1.6:1
	Lama et al (2000)[33]	59	22	37	1:1.7
	Papachristou et al (2006)[36]‡	181	98	83	1.1:1
0-2	Hansson et al (1999)[13]	1953	950	1013	1:1
	Silva et al (2006)[19]§	357	103	284	1:3
0-15	Smellie et al (1975)[20]	233	46	187	1:4
	Lenaghan et al (1976)[24]	102	35	67	1:2
	Bellinger and Duckett (1984)[21]	392	69	323	1:5
	Goldraich and Goldraich (1992)[22]¶	202	43	159	1:4
	Wennerstrom et al (2000)[26]	1221	232	989	1:4
	Merguerian et al (1999)[23]*	240	48	192	1:4
	Silva et al (2006)[19]§	296	64	232	1:4
Adults (>15)	el Khatib et al (1990)[139]	293	49	244	1:5

[*] Radiologic series.
[†] Includes 24 with prenatal diagnosis.
[‡] Includes 5 sibling reflux (excludes prenatal diagnosis).
[§] Includes 2 sibling reflux (excludes prenatal diagnosis).
[¶] Excludes grade V reflux, and patients with obvious dysfunctional voiding.

the more equal the incidence.[8,13] Four times as many girls as boys are identified with VUR during childhood, however (Table 22-1).[13,19-26] The overall picture is that boys present predominately in the first year of life often with severely dilated upper urinary tracts, and often congenital nephropathy (Table 22-2).[23,27-37] Girls present cumulatively throughout childhood and have less upper tract dilation. By age 2 years, the proportion of girls presenting with VUR slightly exceeds boys, but the proportions are more equable; thereafter, girls predominate.[13,19-26]

VUR may have a genetic basis. A meta-analysis of screening studies shows an incidence of 32% among siblings[38] (100% for identical twins[39]); if a parent is affected, the risk increases to 69%.[40] Many different gene candidates are implicated in abnormal ureteral bud development, reflux, and renal dysplasia, but no specific genes have been identified to account for transmission of human VUR (see Chapter 12). The reflux condition is very heterogeneous and not dependent on a single gene disorder.[41] The severity of the reflux and the associated problems can vary within a single family (i.e., the phenotype is variable).[42]

Ureterovesical Junction

The UVJ is structurally and functionally adapted to allow the intermittent passage of ureteral urine and to prevent the reflux of bladder urine. To achieve these functions, the ureter enters the bladder with an oblique intramural passage, which extends submucosally to open onto the trigone (Fig. 22-1).[43]

Reflux is prevented by active and passive components. The natural tonus of the ureteral muscles maintains an active closure of the intravesical ureter except during the efflux of urine.[44] The longitudinal ureteral muscles intermingle with those of the (superficial) trigone and the contralateral ureter so that contraction elongates the submucosal tunnel. The adventitia fuses with a fibrous sheath (Waldeyer) circumferentially, allowing the intramural ureter to move within the hiatus during bladder filling. Recent studies in the fetus and newborn have challenged some of these concepts, but the precise age-specific anatomy is not yet defined.[45]As the bladder fills and becomes distended, there is progressive obliquity of the intravesical ureter; the trigone is progressively stretched, increasing resistance in the intravesical ureter and causing increased pressure within the distal end of the ureter. During micturition, when the trigone is stimulated, the intravesical ureter is pulled downward, and the ureteral walls are compressed against the supporting vesical wall as a passive reinforcement of the valvular mechanism. These actions anchor the ureter, retaining its correct configuration and preventing lateral displacement of the ureteral orifice. The mechanism requires a complex of muscular components that includes ureteral and vesical muscle bundles and an elaborate neural influence. Neurohistochemistry has defined a dual autonomic innervation by cholinergic and noradrenergic nerves, and there is evidence for neuropeptides that may act as neuromodulators.[46-48] Immunohistochemistry has revealed further abundant innervation at the UVJ and numerous nitric oxide synthase immunoreactive nerves that may have a regulatory role, as evidenced from separate biochemical and functional studies.[49]

Ureterovesical Junction and the Genesis of Vesicoureteral Reflux

Immaturity affecting the length of the submucosal tunnel provides a well-accepted explanation for the common occurrence of VUR in young children and its spontaneous resolution during growth. The intravesical ureter (the intramural segment and the submucosal tunnel) has been estimated to lengthen from 0.5 cm in neonates to 1.3 cm in adults; the mature length is achieved by 10 to 12 years of age.[50] There is interspecies and intraspecies variability in the natural incidence of VUR; in animals, this is associated with the length of the intravesical ureter and the degree of trigonal development.[51] Lenaghan and Cussen[52] observed the disappearance of reflux with growth in normal dogs.

In human fetuses, there is a correlation between gestational age, intravesical ureteral wall thickness, and the length of the intravesical ureter.[53] A short intravesical ureter is unlikely to be the only factor associated with reflux in the immature human. Trigonal and distal ureteral muscle deficiency has been noted in children with VUR.[54,55] Studies employing immunohistochemical methods have shown further a reduced

Table 22-2 **Presenting Features in Infant Series with Primary Vesicoureteral Reflux Diagnosed after Prenatal Hydronephrosis**

Series	No. Patients	Males	Females	M:F	% Units Grade IV-V VUR	Congenital Nephropathy
Sheridan et al (1991)[29]	19	16	3	5:1	—	29% patients
Burge et al (1992)[30]	39	30	9	3:1	50	33% patients
Marra et al (1994)[31]	27	23	4	6:1	68	44% units
Yeung et al (1997)[32]	155	117	38	3:1	46	28% units
McIlroy et al (2000)[8*]	69	37	32	1:1	32	10% patients
Nguyen et al (2000)[34†]	34	28	6	5:1	64	41% units
Lama et al (2000)[33]	34	25	9	3:1	75	85% units
Brophy et al (2002)[35]	40	34	6	6:1	38	13% units
Ismaili et al (2006)[37]	43	31	12	3:1	39	24% patients

[*] Screening study of infants with low-threshold prenatal hydronephrosis (anteroposterior pelvis diameter ≥4 mm).

[†] Includes 4 sibling reflux.

VUR, vesicoureteral reflux.

Note: The figures for the incidence of congenital nephropathy should be treated with some caution. Every effort has been made to exclude the infected patients using the information provided by the authors.

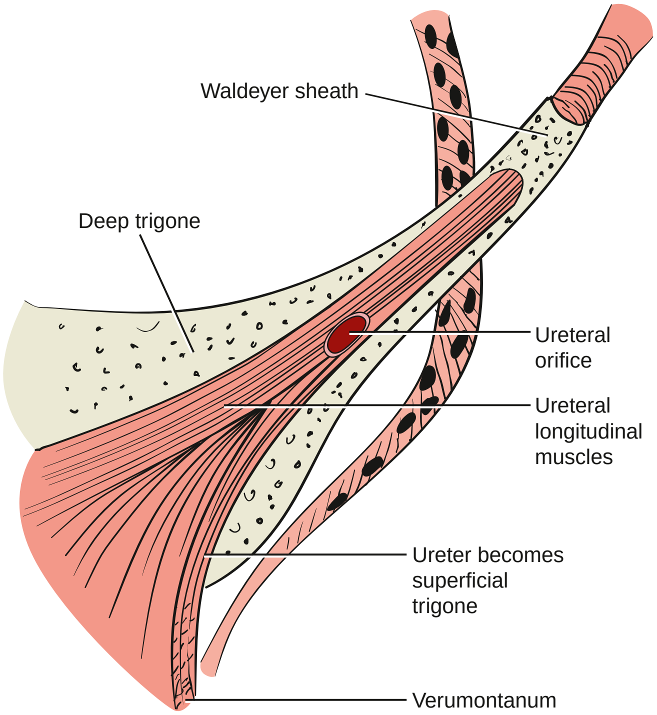

Waldeyer sheath
Deep trigone
Ureteral orifice
Ureteral longitudinal muscles
Ureter becomes superficial trigone
Verumontanum

Figure 22-1 The classical view of the ureterovesical junction. The ureter enters the bladder with an oblique passage to open onto the trigone. There is a seamless continuity between the ureter and the trigone, which extends in males to the verumontanum. The adventitia fuses with Waldeyer sheath. The longitudinal ureteral muscles extend and fuse with the muscles of the opposite ureter to form the superficial trigone. Recent studies challenge some of these concepts (see text). (Adapted from Tanagho EA, Pugh RCB. The anatomy and function of the ureterovesical junction. *Br J Urol.* 1963;35:151.)

nerve supply, a disordered extracellular matrix, ureteral muscle atrophy, and dysplasia at the ureterovesical junction such that symmetric contraction of the smooth muscle coat is not achievable (i.e., there is no active valvular mechanism). Some of the material examined had been subject to prior infection, however.[56,57]

The importance of the functional element in preventing reflux is supported by the finding of absent interstitial cells of Cajal in refluxing ureters. These cells are thought to act as pacemakers for coordinated muscle activity.[58]

Tanagho and colleagues[44,54] emphasized that poor development or a deficiency of the trigone and ureterotrigonal musculature is the predominant cause of reflux. It allows lateral displacement or migration of the ureteral orifice and inevitable reduction in intravesical length.

The lateral displacement of the ureteral orifice reaches its most extreme expression as the classic “golf-hole” orifice, which is associated with free reflux and often with dilated upper urinary tracts. Mackie and Stephens[59] postulated that this displacement represents a primary abnormality of the ureteral bud resulting in a ureter that arises in a laterally ectopic position (Fig. 22-2). The theory has been controversial and considered most plausible when applied to duplex systems. It has now achieved credence with the discovery of specific genes involved in the induction and orientation of the ureteral bud and renal development.[60,61] The subject has been extensively reviewed,[42,62] with evidence indicating that VUR can be a field defect with displacement of the ureteral bud giving rise to the abnormal orifice and ureter, while inducing dysplastic renal development on that side.

There are considerable complex genetic and molecular interrelationships. The angiotensin II receptor gene type 2 *(Agtr2)*, present in humans and animals, has a diverse and extensive regulatory role in the urinary tract. Its inactivation in mice can cause VUR, or renal hypoplasia or dysplasia or both, with ureteral ectopia as part of a spectrum of

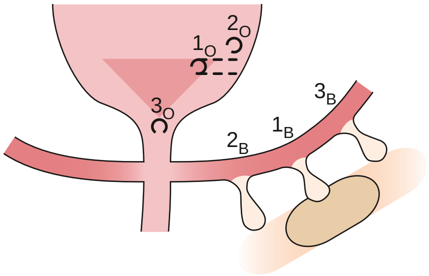


Figure 22-2 The position of the ureteral orifice is determined embryologically by the point of fusion of the ureteric bud before fusion with the mesonephros. The ureterovesical junction may arise at any point between 2 and 3. Position 3—distally ectopic nonrefluxing (when this is situated at the bladder neck or in the urethra, reflux may occur). Position 1—normal nonrefluxing. Position 2—lateral ectopic refluxing. Fully normal differentiation of the renal blastema occurs only when the ureteric bud develops from position 1. (Adapted from Mackie G, Stephens F. Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. *J Urol.* 1975;114:274.)

congenital anomalies of the urinary tract. It seems, however, that other control mechanisms operate that can correct ectopic ureteral budding, such that an "abnormal" ureteral bud in early gestation does not lead to an evident abnormality in mice at birth. The significance of these observations is currently unknown.[61] The mode of inheritance of mutant *Agtr2* is sporadic (i.e., there is incomplete penetrance), and no association has been found between human *Agtr2* mutations and VUR. Instead, multiple genes cooperate to achieve correct development, and a multiplicity of minor genetic aberrations may be required before human VUR is expressed.[62] Such complexity may explain the wide variability of the VUR disorder.

VUR shows a wide spectrum of anatomic and functional abnormalities. At a mild extreme of the disorder, the reflux may appear benign and, unless urinary infection intervenes, exempt from any associated renal pathology. A marginal incompetence may not indicate a pathologic situation, but instead the consequence of normal biologic deviance, such as occurs with other natural physical dimensions. The absence of identifiable VUR in healthy, normal newborn and premature infants suggests that it is not the norm.[3,4] At the tail-end of normal biologic variation, however, shortness in the intravesical ureter or a marginal immaturity in ureterotrigonal musculature may bestow a predisposition to VUR. Tanagho and colleagues[44,54] postulated that a minor trigonal deficiency may result in a marginally incompetent UVJ that permits reflux only when challenged; a moderate deficiency might explain reflux that occurs only with the elevated pressures of micturition, whereas severe deficiency would allow reflux at low pressure.

Primary and Secondary Vesicoureteral Reflux

An abnormal UVJ may arise from maldevelopment, malfunction, or delayed maturity through the mechanisms outlined earlier, and such reflux is regarded as "primary." The UVJ is also affected, however, by changes occurring in the bladder wall as a result of other pathologies, such as outflow obstruction, which may disrupt the normal mechanisms, allowing reflux to occur; this is often referred to as "secondary" reflux. These are simplistic divisions and in clinical terms may be unimportant. The boundaries become blurred when primary reflux at the severe end of the spectrum also is found to be associated with primarily abnormal bladder function (see later), and when a marginally competent UVJ is disrupted by infection.

Confusion also arises from the historical terms "low-pressure" and "high-pressure" reflux because the worst renal prognosis is often seen in the low-pressure group.[63-65] The terminology arose as a result of the most severe primary cases showing reflux occurring freely from early in the filling phase through golf-hole orifices into highly abnormal kidneys. Conversely, high-pressure reflux was a secondary event occurring at high bladder pressures either late in filling or in voiding when bladder function was abnormal and finally overcame the resistance at the UVJ. If this reflux occurs into a developmentally normal system, such kidneys might be more at risk for damage by acquired lesions (see later).

Spontaneous Resolution

The spontaneous resolution of VUR during childhood accounts for its greater prevalence in neonates than older children,[66] and contributes to its scarcity in adults.[67] A study following adults since childhood VUR showed reflux persisting after adolescence in 53 of 221 (24%).[68] The grade of reflux influences, but does not determine, whether or not reflux disappears, the rate of which may be 85% for radiographically low-grade reflux and 41% for severe reflux.[66] Resolution is more likely, or occurs sooner, the younger the child is at diagnosis.[19,69] In one infant series, the resolution rate at age 15 months was 70% for mild reflux and 43% for severe reflux.[32] By way of contrast, the International Reflux Study reported a 28% resolution rate after 5 years and 47% after 10 years for their older population at the outset with grades III and IV reflux.[69,70] Boys have a faster resolution rate than girls, regardless of grade and age of series studied.[19,71,72]

Dynamics

Micturating cystourethrography, introduced in the 1920s, remains the standard diagnostic investigation for VUR. It shows reflux from the retrograde egress of radiographic contrast media instilled into the bladder during radiographic screening. The passage of contrast media may be observed to pass into the ureter only or to extend to the renal pelvis. The upper tracts may appear normal or grossly dilated and distended. These radiologic appearances form the basis for an internationally accepted five-point classification scheme (see Chapter 23).[73]

The diagnostic emphasis on the anatomic features, portrayed by the micturating cystourethrogram, creates a concept that reflux is a passive event, when in reality it is the consequence of lower urinary tract dynamics. In everyday life, the reflux of urine from the bladder occurs only when bladder pressure exceeds ureteral pressure (i.e., in association with detrusor muscle contraction), and this could be an isolated unstable contraction or a full voiding episode (Fig. 22-3). Experience with cystography combined with simultaneous pressure and flow studies has supported this view and shown it to be true even in the presence of grossly dilated systems showing apparently "low-pressure" reflux diagnosed on conventional contrast cystography alone.[74-76]

The contrast examination is totally artificial in that it fills a completely emptied and collapsed system from below. Although excellent at showing anatomic features, such as upper tract dilation or paraureteral diverticula, it cannot emulate normal antegrade filling. The difference in dilation, upper tract drainage, and the reflux event (timing and volume) shown by direct contrast cystography and physiologic indirect cystography in the same patient can be startling. Upper

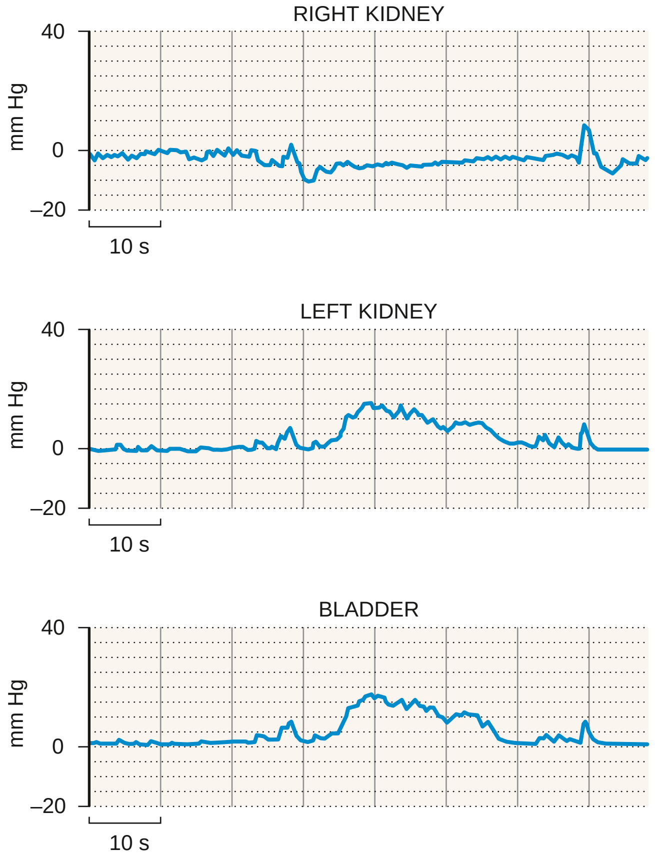


Figure 22-3 Transmission of intravesical pressures to the left renal pelvis in the presence of left vesicoureteral reflux. The cystometrogram was obtained during micturition in a pig. (From Ransley PG. Intrarenal reflux: anatomical, dynamic and radiological studies, part I. *Urol Res.* 1977;5:61. Copyright © 1977 Springer-Verlag.)

tract dilation may be developmental in the dysplastic sense—derived from an abnormal ureteral bud and not occurring secondarily as a result of the urodynamic consequences of reflux. The actual "reflux" feeding back into such a system may be no "worse" than reflux feeding into a nondilated system.

Combined urodynamics and isotope cystography has identified subtle variations in the reflux event indicative of a range of functional abnormalities. In some ureters, the reflux does not occur at peak detrusor pressure, but only as the detrusor begins to relax, and pressures are declining. This situation contrasts with other ureters when reflux occurs at the peak voiding pressure or throughout voiding from the moment that voiding pressure begins to increase.[75] These distinctive patterns may reflect different etiologic forms of VUR and trigonal deficiency or dysfunction.

These fundamental considerations of the dynamics of reflux and the possibly independent anatomic abnormalities seriously question the validity of the conventional grading system for reflux. Although it is true that the big dilated ureters are often associated with the worst kidneys (which we now believe to be mostly affected by congenital nephropathy), it is possible that a sustained squirt of high-pressure infected reflux into a nondilated ureter may present the greatest potential for acquired renal scarring. It is inappropriate to think of dilated ureters as a pressure sink that can absorb the pressure of reflux. This concept derives from the retrograde filling technique of contrast cystography. In real life, the ureter fills from above, and toward the end of this filling the ureters are full as the reflux event begins.

The open communication between the pelvicalyceal system and the bladder via the ureters exposes the kidney to bladder pressures (see Fig. 22-3) and to bladder dysfunction. Any *sustained* pressure elevation resulting from poor bladder compliance or prolonged and frequent voiding creates an obstructive situation. At the extreme, this elevated pressure can cause damage by an obstructive mechanism in the absence of infection. In the presence of obstruction, or persistent obstructive dynamics, such as occurs with bladder dysfunction, the kidney is extremely vulnerable to the introduction of infection just as it is in any obstructed system.

Summary

We may form an overall picture of the reflux problem in our minds. There is a group of children, predominantly male, with golf-hole orifices, dilated ureters, and abnormal kidneys as the result of ureteral bud maldevelopment. Beyond this, there is a large population of children with abnormal, or marginally abnormal, UVJs (in either the physiologic or anatomic sense), which is equally common in boys and girls. Some event is required to unmask the reflux, and this may be bladder dysfunction, urinary infection, or both. Because urinary infection is the most common event, and this occurs most commonly in girls, it has given the impression that reflux is more common in girls. It is probably the vulnerability to urinary infection that gives rise to the apparent female predominance, however. It is as logical, and probably more so when noting that in a population of children with urinary infection 30% to 50% show reflux, to conclude that infection is the factor triggering VUR, rather than the preexisting VUR being the factor predisposing to infection. This conundrum is too difficult to handle in the clinical arena, and the classic view of reflux predisposing to infection firmly prevails against all logic.

Salient points regarding the anomaly of VUR are as follows:

- VUR occurs as the result of disordered ureterotrigonal anatomy.
- VUR may be transient through immaturity.
- VUR may be a congenital anomaly with variable expression, which may be potential, mild, or severe.
- An additional stress factor at the UVJ may be required to promote VUR.
- Resolution or diminution of the reflux occurs with time.

PATHOPHYSIOLOGY OF VESICOURETERAL REFLUX

Many indicators begin to point to a genetic basis for VUR. If this is the case, it can be presumed that the condition exists at birth. It follows that detection of an asymptomatic reflux patient in early life should allow the clinical evolution to be traced until the patient presents symptomatically later in life in a classic manner. This does not seem to happen, and it is now being recognized that there are different groups of reflux patients: (1) patients diagnosed in infancy, usually boys after identification of prenatal abnormality and more obviously genetically determined, and (2) patients, mostly girls, presenting later in childhood and often associated with dysfunctional voiding or urinary infection or both. A problem is that many of the index cases that lead to family studies supporting the genetic concept come from the second group, and the key to this conundrum may be a genetically determined predisposition to urinary infection, which generates dysfunctional voiding (or vice versa).

Immature Bladder

Development of Lower Urinary Tract Function

The immaturity of the bladder and the mechanisms controlling it are extremely complex, involving multiple reflex arcs and input from the higher centers. The development of complete peripheral neuronal integration and volitional control is essential for attaining coordinated micturition and mature bladder function.[77,78]

A normal immature bladder of infancy has the same low-pressure bladder filling and storage characteristics as a normal mature bladder. Detrusor overactivity with filling is rare. During voiding, maximum voiding pressures are higher than in maturity in boys and girls, although more markedly elevated in boys.[78-80] There can be incomplete detrusor/sphincter synchrony during voiding, which results in an interrupted urinary flow with intermittent high bladder pressures as the detrusor contracts against a closed or only partially relaxed sphincter (Fig. 22-4).[78,80,81] This immature incoordination differs from the classic dysfunctional voiding of later childhood in that the immature bladders empty efficiently leaving little or no residue, and they do not feature instability.[78,80]

In a group of 6-month-old infants, half showed urodynamic evidence of immature voiding, whereas voiding observational studies in healthy infants have shown immaturity as interrupted voidings in 20% that persists until 2 years of age.[79,82] In a normal infant, bladder control develops progressively so that complete voluntary control of micturition is achieved by 2 to 4 years old.[83] In some infants with reflux, bladder function also normalizes. In others, an abnormal pattern may persist, or progress in severity, into childhood; such observations raise questions about the impact of reflux itself in the evolution of bladder function and the nature of congenital bladder dysfunction.[79,84-88]

Immature Voiding Dynamics, Vesicoureteral Reflux, and Urinary Infection

Immature voiding dynamics together with marginal competence of the UVJ may determine whether or not VUR occurs. A concept consistent with observations is that infants with VUR have higher voiding pressures overall than infants without VUR, even when bladder function is otherwise normal, although immature.[79] The gradual maturation of voiding dynamics during the first 2 years may account for the early resolution of infantile VUR.[32,71,88]

Infection may add a further component to the balance between bladder function and the reflux event in infants. Bachelard and colleagues[89] found detrusor overactivity after urinary infection in two thirds of infants younger than 1 year, of which half had VUR. Bladder dysfunction and recurrent urinary infection significantly delay the resolution of infantile VUR.[71]

Newborn and Infant Reflux Population

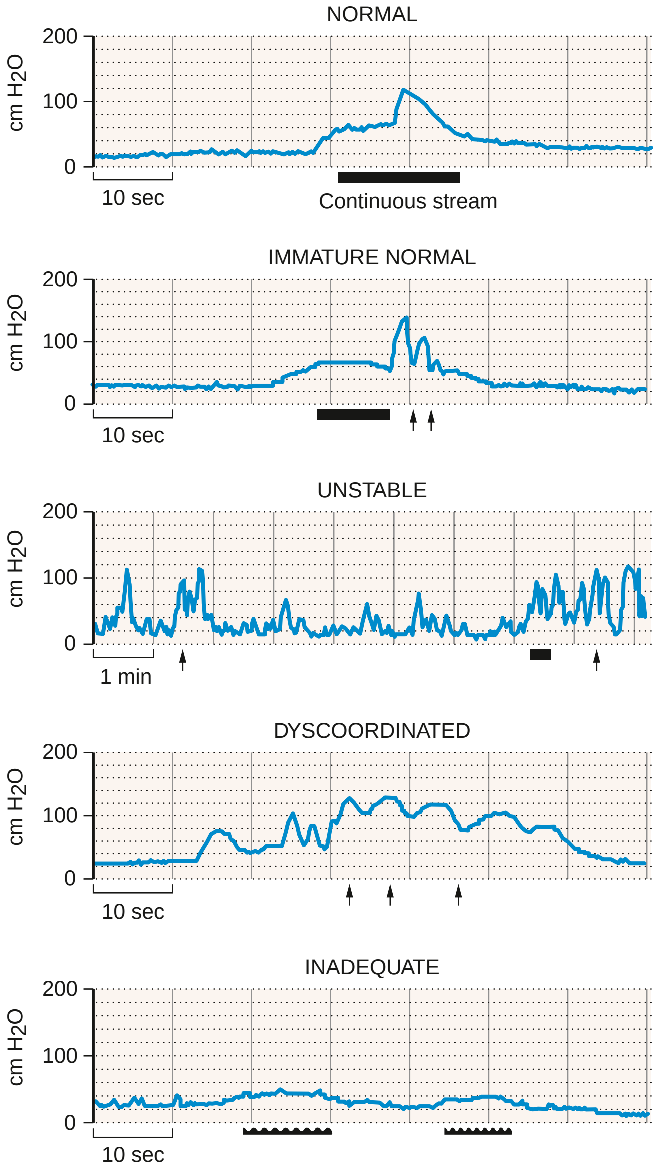


Figure 22-4 Patterns of voiding dynamics in infants with vesicoureteral reflux showing normal, immature, and abnormal patterns compared with infants with normal bladders and without reflux. With immature voiding, a continuous urine stream *(blocks)* gives way to a brief episode of interrupted urine flow *(arrows)* associated with a sharp increase in detrusor pressure as a result of immature detrusor/sphincter asynchrony. These asynchronous episodes are exaggerated in unstable and dyscoordinated patterns. (From Yeung CK, Godley ML, Dhillon HK, et al. Urodynamic patterns in infants with normal lower urinary tracts or primary vesico-ureteric reflux. *Br J Urol.* 1998;81:461.)

Newborns and infants with reflux are of central interest at present, and data from these patients have challenged many long-held presumptions about reflux and associated renal damage or reflux nephropathy. Although reflux from birth may occur equally in boys and girls (see earlier), the sexes differ insofar as the boys are commonly affected by higher grades of reflux and associated renal abnormalities (Fig. 22-5).[32] Much of what follows has been learned from focusing on this latter group. Their characteristics support the concept of VUR as part of a field defect that includes bladder function, the integrity of the UVJ, and the renal parenchyma. This concept has led to recognition that much of the severe renal "scarring" associated with reflux is present at birth and purely dysplastic or hypoplastic in origin.[90,91]

Abnormal bladder function is common in infants with dilating reflux, even in the absence of urinary infection. In a

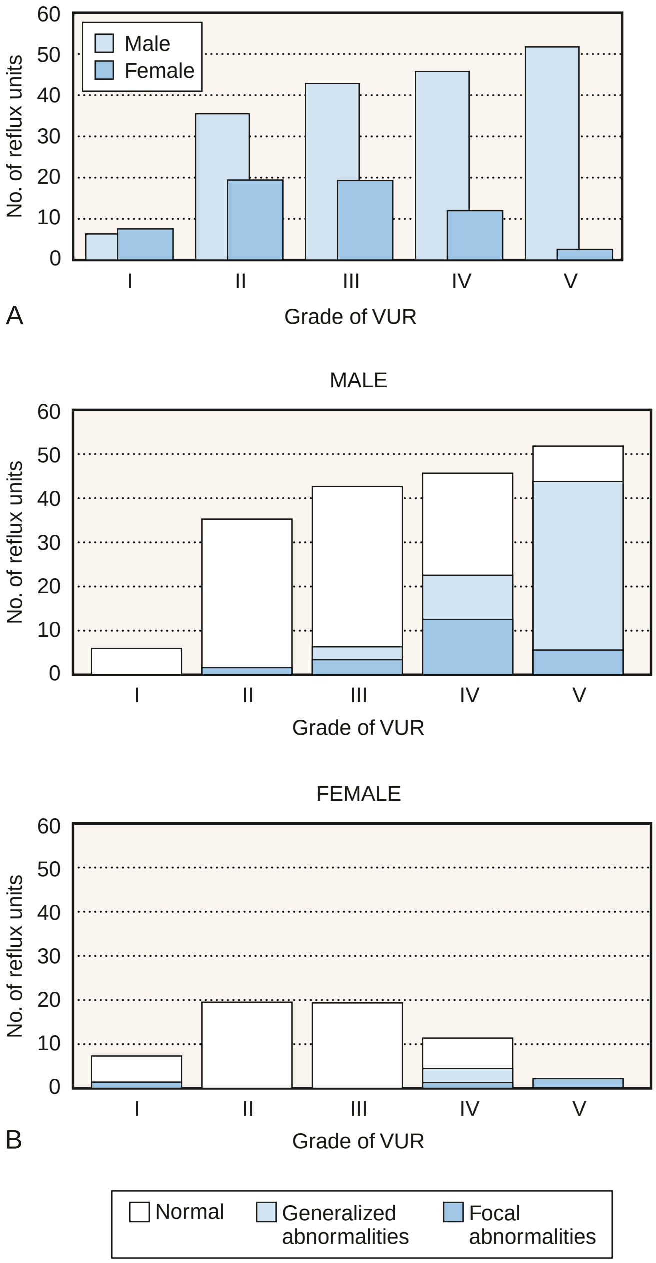
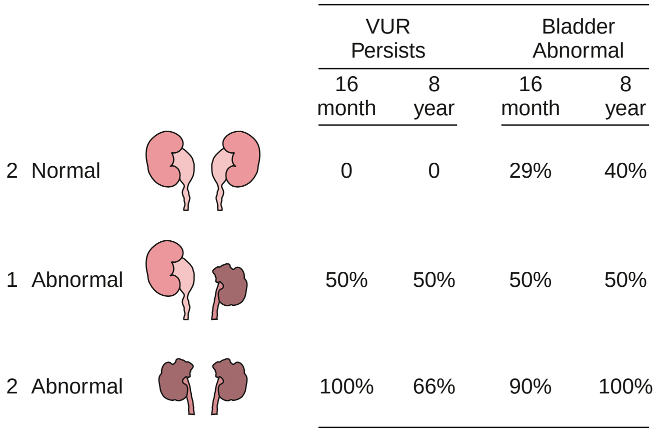


Figure 22-5 **A,** Distribution of grade of vesicoureteral reflux (VUR) among male and female infants identified by prenatal hydronephrosis. **B,** Distribution of nephropathy among male and female infants (study population as in **A**). (Adapted from Yeung CK, Godley ML, Dhillon HK, et al. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. *Br J Urol.* 1997;80:319.)



	VUR Persists		Bladder Abnormal	
	16 month	8 year	16 month	8 year
2 Normal	0	0	29%	40%
1 Abnormal	50%	50%	50%	50%
2 Abnormal	100%	66%	90%	100%

Figure 22-6 Persistence of vesicoureteral reflux (VUR) and evolution of bladder function in a population identified by prenatal ultrasound and followed for 8 years. (From Godley ML, Desai DY, Dhillon HK, et al. Outcome of bladder function and vesicoureteric reflux at 8 years in children previously investigated at 16-month age. *BJU Int.* 2001;87[Suppl 1]:58 [Abstract].)

controlled study of 42 infants (36) with dilating VUR, most with prenatal diagnosis and no history of urinary infection, Yeung and associates[79] found 57% had abnormal urodynamics. Compared with 16 control infants with normal urinary tracts, a spectrum of bladder dysfunction was observed in both sexes. The boys with VUR had higher voiding pressures than control infants without VUR and featured detrusor overactivity with small functional (voiding) capacity or an inadequate detrusor contraction with micturition, which was not seen in girls. Other infants had pronounced dyscoordinated voiding also associated with detrusor overactivity. This latter finding was similar to the "hypercontractile" bladders described by Sillen and coworkers[92] and found in boys.

The abnormal features of male urodynamics are consistent with a possible transient obstructive event in utero.[79] This concept conveniently explains the male preponderance for prenatal hydronephrosis, postnatal ureteral dilation, and increased bladder wall thickness compared with girls. A transient obstruction, perhaps resulting from delayed maturity of the external sphincter,[93] that induces a "secondary" reflux also might explain why male infants with VUR resolve reflux earlier than their female counterparts.[71]

In a follow-up series of 40 infants (32 boys) with dilating reflux, the degree of renal abnormality correlated with the presence of bladder dysfunction and inversely with the rate of reflux resolution (Fig. 22-6). In infants with two normal kidneys, the reflux resolved in 100% by 16 months of age with only 30% showing urodynamic abnormality of detrusor overactivity. By contrast, the presence of two abnormal kidneys correlated with an abnormal bladder in 90%, which persists to age 8 years, together with 30% resolution of VUR. The bladder dysfunction seen in the older boys with bilateral abnormal kidneys had features of a "lazy," inadequately emptying bladder.[88,94]

The presence of two normal kidneys at the outset of life may be useful as a marker to aid prediction of early reflux resolution and obviate the need for bladder investigation. The long-term follow-up does not lead, however, to a classic population of refluxing young children with urinary infection, most of whom have normal kidneys.

The situation is different for patients with abnormal kidneys at the outset. The 8-year outcome of a "lazy" bladder associated with bilateral nephropathy is in keeping with other observations. Griffiths and Scholtmeijer[84] also showed various patterns of urodynamic abnormality in older children with VUR: unstable bladders correlated with unilateral reflux and normal upper tracts; a poorly contractile detrusor muscle correlated with bilateral reflux and abnormal upper tracts or renal abnormalities. Detrusor failure was attributed to the long-term outcome of voiding dysfunction. The inadequate bladder of boys with severe bilateral VUR seems to be the outcome of "hypercontractile" or severely dyscoordinated micturition in infancy. This progression was documented by Sillen and coworkers[86] during early life. Yeung and colleagues[79] reported the presence of an inadequate detrusor as early as 6 months of age in some male infants with VUR. Its preponderance by 16 months of age indicates that the evolution of detrusor failure occurs quite rapidly and in early infancy.[88]

Urinary Infection and Reflux in Older Children

The classic reflux patient is identified as a result of investigation after one or more episodes of urinary infection. Under such circumstances, 30% of older children show reflux of varying severity, most of which are lesser degrees into nondilating systems. Most are girls because identification depends on urinary infection.[10-12,19,72] There is a long established concept that reflux promotes urinary infection as a result of the residual urine that it creates. There is much to challenge this view, however. A long-term follow-up study into adult life of 226 children (189 girls) showed that urinary infection recurred in 49% of these patients as adults regardless of the presence or absence of renal scarring, and whether or not VUR was persistent at the end of childhood.[68] These findings are supported by controlled studies that show infection rates are similar in the surgical and nonsurgical arms, although more symptoms of upper tract colonization occur in patients with ongoing reflux.[69,95,96]

It seems more probable that the functional abnormality lies in an individual's susceptibility to urinary infection, which then effects changes to bladder, ureteral, and trigonal function with resultant reflux. The molecular basis for host vulnerability to urinary infection is under intense investigation, and genetic variations in blood group, receptor mechanisms, and neutrophil function have been identified. The subject is well reviewed by Svanborg and colleagues.[97]

There is a strong but circular and complex relationship between VUR, urinary infection, and bladder dysfunction. There are often concomitant bowel problems, which have led to the term *dysfunctional elimination syndromes* (DES).[98] In a series of 143 children with VUR, reported by Koff and associates,[99] DES was present in 43% with "primary" VUR and 77% of a subset with recurrent urinary infection. Bladder dysfunctions delay the resolution of VUR, adversely affect the success of reimplantation, and increase the risk for recurrent urinary infection.[71,99,100]

Infection greatly distorts bladder function and may be the factor in initiating many cases of DES, whereas others have no identifiable cause. Chen and colleagues[101] concluded from a large multivariate analysis that the presence of urinary infection had a significant impact on the occurrence of DES in patients with VUR. Of 2759 patients, DES occurred in a greater proportion of girls (44%) than boys (24%). Contrary to previous beliefs, however, it was not associated with urinary infection or VUR independently. The occurrence of DES correlated only when urinary infection and VUR were present together in the same patients.

Bladder instability, or detrusor overactivity, causes urgency, wetting, and a small functional capacity. Although there are reports showing no statistical association between reflux and detrusor overactivity,[84] it is easy to comprehend how it might aggravate a marginal UVJ to cause reflux. It has been observed that a detrusor contraction during filling can initiate the reflux event.[74,84,102] Instability can occur in 60% of children with VUR,[103,104] but its overall clinical role is difficult to interpret because the instability and the reflux may resolve with time. Taylor and associates[105] found that bladder instability did not influence the resolution rate of VUR in girls. A controlled study of children with VUR and unstable bladder showed more encouraging results. The anticholinergic agent oxybutinin chloride produced a significantly decreased detrusor contractility index and decreased the degree of reflux.[106] Such data support reports that in the presence of instability, reflux resolves more rapidly with, than without, appropriate anticholinergic medication.[107]

The strong association between dysfunctional voiding and urinary infection and the further association with VUR suggest that reflux itself can be "acquired." A preexisting trigonal abnormality may be necessary for VUR to be acquired, allowing reflux to be precipitated by infection or abnormal bladder function.

Experimental Pathophysiology of Urinary Infection

The role of infection in inducing reflux has been debated since Tanagho and colleagues[44] proposed that inflammation might challenge a mildly deficient UVJ to initiate reflux. In extreme circumstances, complete destruction of the UVJ occurs in pregnant sows with urinary infection by *Corynebacterium*.[108] More analogous to the human situation, reflux was reportedly acquired, probably by a nonspecific inflammatory response, in six of seven experimental piglets (female) after institution of urinary infection with *Escherichia coli* of the types responsible for human urinary tract infection.[109]

Human urinary infections are caused by specific strains of *E. coli*, with a limited range of O serotypes and P-fimbrial expression for attachment to epithelium.[97,110] Bacterial adherence and pathogen recognition by the host triggers the innate epithelial cell response. The bacteria cause a direct, rather than inflammation-mediated, disruption to the physiologic activity of urinary tract muscle by endotoxin-mediated inhibition of α-adrenergic receptors; the latter is observed during in vitro studies of the outlet (trigonal) region of the cat's bladder.[111] A similar effect on the ureter may explain the ureteral dilation and disturbed peristalsis observed in humans[112,113] and animal models.[110] Experimental work using the monkey led Roberts and colleagues[114] to propose that P-fimbriated *E. coli* can ascend the upper urinary tract by progressive ureteral colonization even in the absence of VUR. A local neurogenic effect of bacterial infection in humans might influence ureterotrigonal dysfunction, facilitate reflux, or encourage ascending infection by a direct effect on the ureter.

Genomics: The Molecular Basis of Vesicoureteral Reflux

Molecular and genetic studies have emphasized the polygenic nature of the reflux disorder, and they may have the potential to explain the different forms or subtypes of the reflux problem overall. Deletion of the *Agtr2* gene in mice can cause VUR and affects only a small proportion of males with low penetrance. It is associated with various anomalies of the urinary tract, such as renal dysplasia and hypoplasia, duplex ureters, and ureteropelvic junction obstruction.[115]

Experimental deletion of uroplakin III, one of a family of genes involved in the normal development of urothelium, affects both sexes equally in causing VUR without promoting other forms of congenital urinary tract anomalies.[116] The human uroplakin genes are only weakly associated with VUR, however, and cannot have a simple dominant role, although they may act as contributory genetic factors.[117] In this latter role, these genes possibly offer an attractive hypothesis as one of the factors associated with a genetic predisposition to bacterial colonization because the urothelium functions as the primary barrier to infection. These two examples, the first analogous to the severe form of reflux with congenital nephropathy and the second analogous to the more common form of VUR associated with urinary infection, highlight the necessity for having carefully defined and stratified populations when sampling for clinical genetic studies.

Molecular studies of bacterial and host interaction indicate several ways in which host genetic variation may affect human susceptibility to urinary infection; for example, a correlation exists between the P1 blood group phenotype and susceptibility to urinary tract infection, and between blood group nonsecretor status and pyelonephritis in patients with VUR.[97] The predominant subtype of the VUR disorder is that associated with urinary infection, and it poses a high risk of potentially preventable acquired renal disease. Human genome studies that seek to identify high-risk factors to infection would seem the most beneficial direction for collaborative investigation. It is not reflux itself that poses the clinical problem; it is urinary infection. Human genome studies unraveling the genetic basis of VUR itself are better directed toward the small proportion of boys who present with congenital nephropathy and have the greatest, although not exclusive, risk of end-stage renal failure.

Proteomics: Molecular Indices of Vesicoureteral Reflux

The urothelium has secretory function and is responsible for numerous soluble proteins in urine. Genetic mutations associated with VUR have the potential to perturb the urothelial structure and function resulting in signature patterns of proteins in the urine. Differential analysis of component urinary proteins using a sophisticated application of mass spectroscopy has found a unique fingerprint (or profile) in the urine from children with reflux nephropathy.[118] The subject is under current investigation with the aim of identifying specific diagnostic markers for VUR and the associated nephropathy. The advancing techniques offer an advantage over traditional methods that consider only concentrations of an individual marker or markers that often have large normal ranges and lack sensitivity and specificity. They also hold a potential to contribute to etiopathogenesis with a greater discriminating power to overcome the confounding effects of infection and renal scarring and to distinguish between the causal and resultant elements. These difficulties have long besieged the search for pathogenetic indices of VUR; for example, *N*-acetyl-D-glucosaminidase (NAG), elevated with tubular damage, has been subject to considerable investigation without any overall consensus of opinion, although evidence points to an association with established renal scarring.[119]

In addition to urinary markers, there can be altered expression of serum proteins in the presence of VUR. There is currently interest in a vascular cell adhesion molecule (VCAM-1) that is elevated with severe VUR regardless of the presence or absence of scars.[120]

Summary

Salient points regarding the pathophysiology of VUR are as follows:

- VUR may have a complex genetic basis.
- Infants with reflux but without infection display a spectrum of disordered bladder function.
- Congenital reflux with normal kidneys resolves early in life.
- The most severe congenital reflux is associated with abnormal kidneys and an abnormal bladder in keeping with a field defect.
- VUR, urinary infection, and DES are closely linked. Any one of them may trigger the others and create the clinical problem leading to infection and renal scarring.
- Continuing molecular studies of bacterial-host interaction may shed light on the relationships between urinary infection, DES, and VUR.

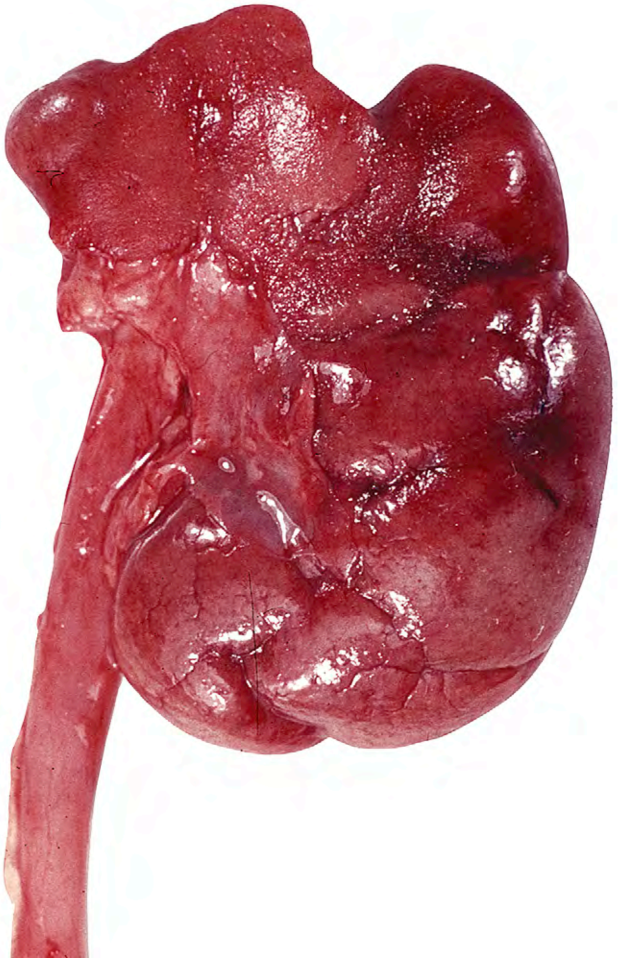


Figure 22-7 Reflux-associated nephropathy in a human nephrectomy specimen.

REFLUX-ASSOCIATED NEPHROPATHIES

The term *reflux nephropathy* was introduced in 1973 to emphasize the association between VUR and the coarse renal scarring previously known as "chronic atrophic pyelonephritis" (Fig. 22-7).[121] Congenital reflux nephropathy may arise through several mechanisms affecting the developing kidney and manifests a spectrum of abnormalities. Genetic defects may have an impact on renal development at different stages, and the embryonic renal development is very sensitive to urinary tract obstruction whether it is transient, prolonged, or permanent.[122-124] The induction of dysplasia by ureteral obstruction is a classic observation in experimental urology.[125] Sterile scarring through an obstructive mechanism can contribute significantly to congenital reflux nephropathy, but plays little part

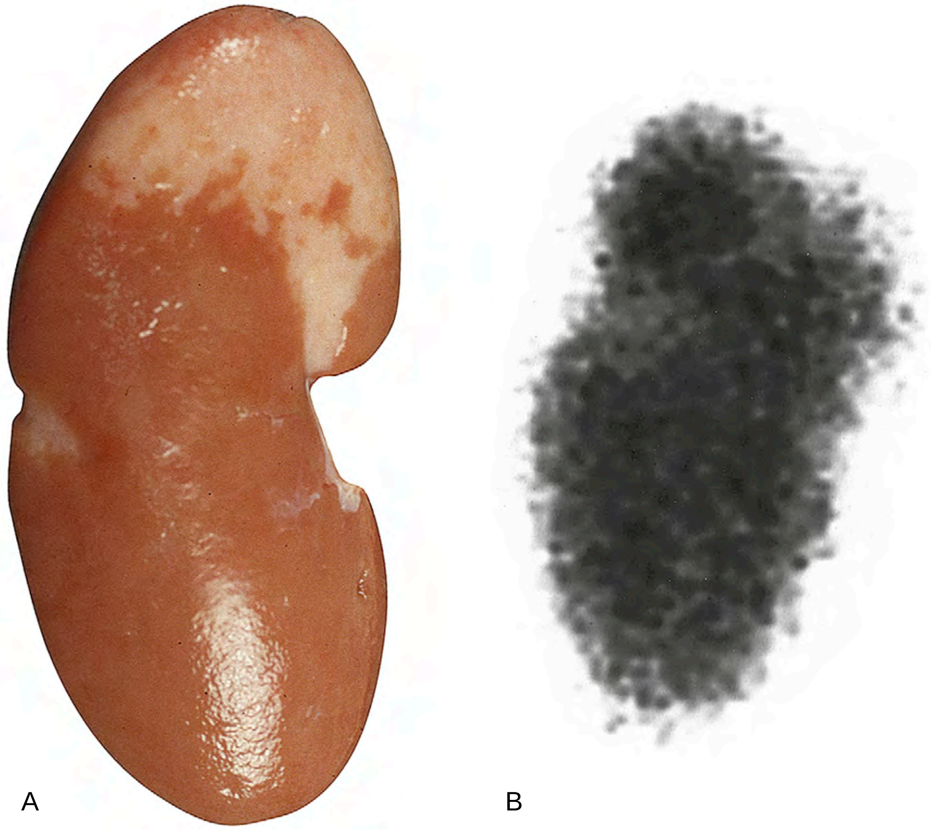


Figure 22-8 Acquired reflux-associated nephropathy. **A,** Newly established focal scarring in a young pig (1 month after instituting urinary infection). **B,** Corresponding appearance with Tc^{99m} DMSA scintigraphy. (Adapted from Risdon RA, Godley ML, Parkhouse HF, et al. Renal pathology and the 99mTc-DMSA image during the evolution of the early pyelonephritic scar: an experimental study. *J Urol.* 1994;151:767.)

postnatally when infection mechanisms dominate.[123,126] The acquisition of renal scarring through the association of reflux, urinary infection, and intrarenal reflux has been observed clinically and experimentally.[126-128]

Radiologic Detection and Characteristics

Renal scarring was originally defined by the appearances on an intravenous urogram and included calyceal and parenchymal abnormalities. This modality has been superseded by the technetium 99m dimercaptosuccinic acid (Tc^{99m} DMSA) scan, in which scars are seen as defects in isotope uptake. The two methods are not always comparable making comparison studies difficult. The Tc^{99m} DMSA scan is a highly sensitive tool for imaging parenchymal involvement in acute pyelonephritis and its evolution to recovery or permanent scarring.[129-133] In experimental studies, established scars were seen as focal defects with a distorted renal outline (Fig. 22-8), allowing others with an intact renal outline to be differentiated as acute defects (Fig. 22-9).[134]

The Tc^{99m} DMSA scan has allowed the recognition that many children with reflux nephropathy identified by prenatal ultrasound have established renal abnormalities in infancy before any urinary infection has occurred. In this group, the kidney may be small, show diffusely poor Tc^{99m} DMSA uptake, or have focal defects, or combinations of all three abnormalities.[23,32,91,135] Renal dysplasia and hypoplasia has been confirmed histologically in the most severely affected kidneys.[135-137] Ultrasound may predict a renal parenchymal abnormality on Tc^{99m} DMSA scan from the observation of size, lack of corticomedullary differentiation, and hyperechogenicity.[91,135]

Pathology

Reflux nephropathy is characterized by its macroscopic appearance. The definitive features are coarse segmental scars, involving cortex and medulla, overlying dilated (or clubbed) calyces. The wedges of fibrous tissue that constitute the scars are sharply demarcated from the surrounding normal renal parenchyma, and scar contraction with hypertrophy of the unaffected renal parenchyma can cause an uneven “lobular” appearance of the renal outline. The renal poles are often more prominently affected.[126] The major changes are interstitial with chronic inflammatory cell infiltration and lymphoid follicle formation together with tubular atrophy and interstitial fibrosis. The full range of histopathologic detail is elaborated elsewhere.[138] In addition, there is a diffuse form of reflux-associated nephropathy that historically was poorly detected by intravenous urography, but was shown by renal biopsy to feature interstitial fibrosis, as with focal scarring. It is clinically significant and is associated with urinary infection, hypertension, and renal failure.[139]

In contrast to these forms, some nephrectomy specimens of reflux-associated nephropathy have shown evidence of renal hypoplasia or dysplasia, indicating a component attributable to abnormal renal development.[137,138,140] These

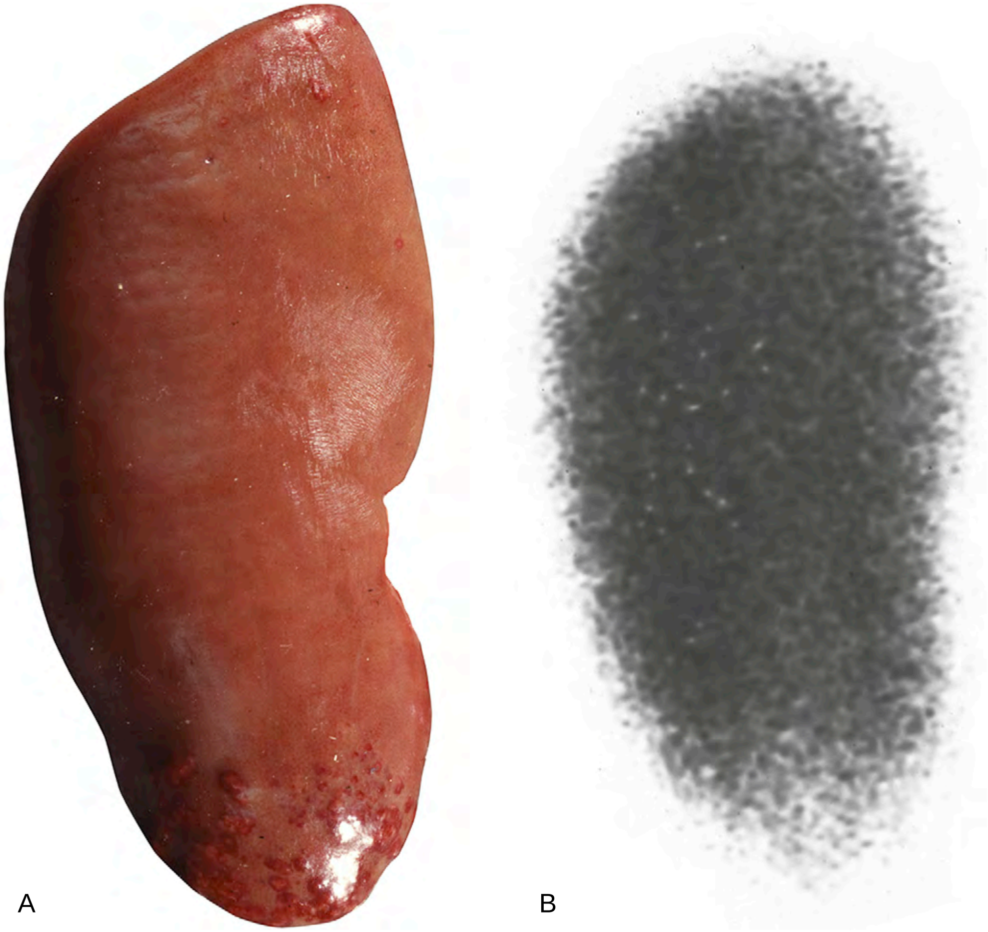


Figure 22-9 Acquired reflux-associated nephropathy. **A,** Early lesion with coalescent microabscesses during acute pyelonephritis in the pig. **B,** Corresponding appearance with Tc^{99m} DMSA scintigraphy (<18 hours earlier). (Adapted from Risdon RA, Godley ML, Parkhouse HF, et al. Renal pathology and the 99mTc-DMSA image during the evolution of the early pyelonephritic scar: an experimental study. *J Urol.* 1994;151:767.)

observations can explain the dysmorphic kidneys seen on Tc^{99m} DMSA imaging in very young infants who have not been exposed to urinary infection. In an examination of nephrectomy specimens from children with VUR, Risdon[138] found focal and segmental dysplastic elements in 63% of 34 kidneys from boys, but not in any of the kidneys from 6 girls. This observation is consistent with the male prevalence for dysmorphic kidneys seen in association with severe reflux in infancy.

Demographics

Hodson[141] estimated that reflux nephropathy affected 1 in 300 in the white population. Thirty percent to 60% of children with VUR have abnormal kidneys, and most of these are present when VUR is first diagnosed. Conversely, even severe grades of reflux in boys and girls can be associated with normal kidneys.

New scars can develop in previously unscarred kidneys. The International Reflux Study[142] reported a 14% incidence during the first 5 years of follow-up regardless of medical or surgical management of VUR. New scarring during the subsequent 5 years was rare, however.[69] As the reflux resolves with time, an increasing number of children are left with persistent scarring in nonrefluxing systems.

In series including older children, a nephropathy is present in similar proportions of boys and girls with VUR, although boys are more severely affected.[135,143] Approximately four times as many girls as boys have "reflux nephropathy," however, accountable by the higher prevalence of the VUR disorder in girls. Bilateral nephropathy is a high-risk factor for chronic insufficiency[144] and the development of hypertension, although hypertension can occur with unilateral disease independent of the degree of scarring.[145] As noted previously, the indications are that male patients are more likely to have the congenital types of nephropathy, whereas female patients are more likely to have acquired renal scarring (see Tables 22-1 and 22-2). The evidence is largely circumstantial, but it is substantiated from observations in series of infants with prenatal hydronephrosis, who are predominantly male. Most of these infants have not had urinary infection, but one third to one half of them have abnormal kidneys on Tc^{99m} DMSA imaging. They are frequently, but not inevitably, associated with the severe (grade IV or V) VUR that predominantly affects boys, and most feature generalized abnormalities typifying dysmorphic kidneys thought to be congenital.[31-34,146] Yeung and colleagues[32] noted that girls with severe VUR were just as likely as their male counterparts to have the congenital type of nephropathy. Fewer infant girls are identified with severe VUR, however (see Fig. 22-5).

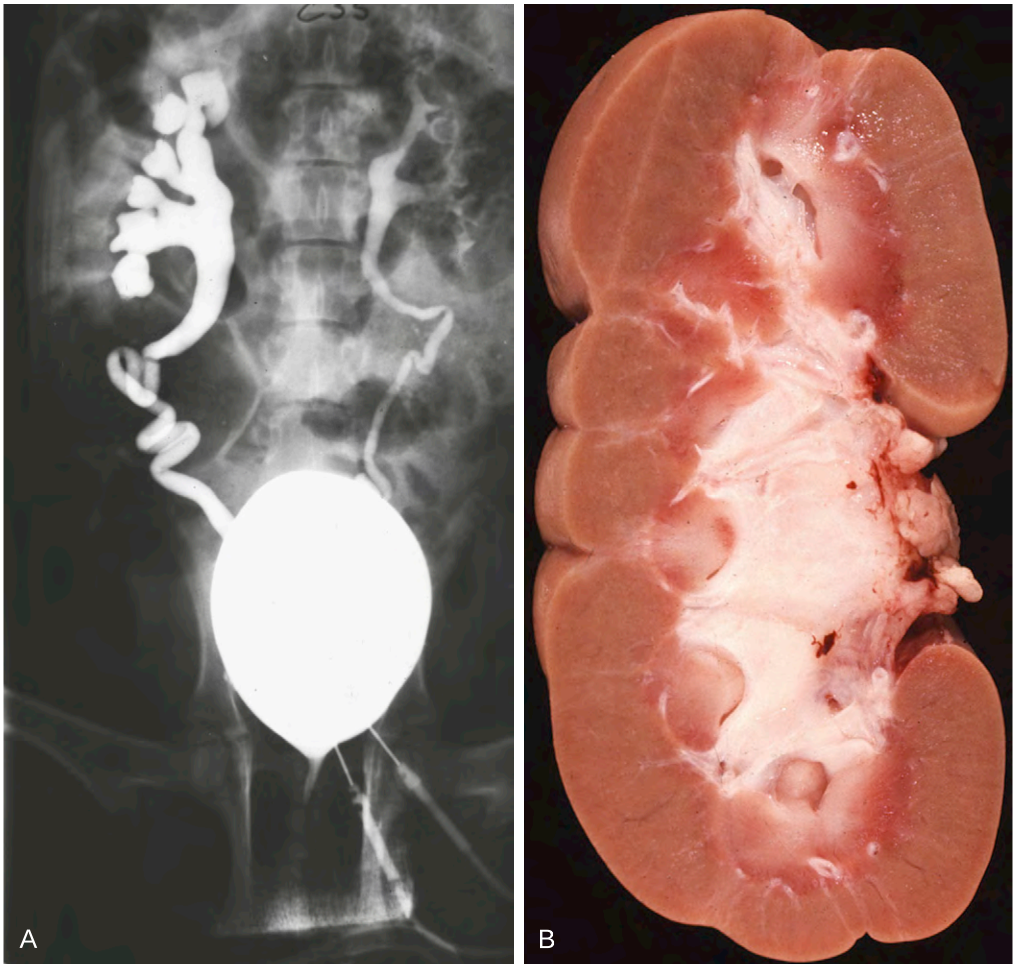


Figure 22-10 Intrarenal reflux and the genesis of focal (segmental) scars. **A,** Cystogram in a pig with right-sided vesicoureteral reflux shows intrarenal reflux. **B,** Same kidney with corresponding segmental scars after the genesis of scarring followed by growth. There is scar contraction. (From the collection of the late C.J. Hodson.)

A radiologic series of 368 patients with primary VUR presenting clinically, most with urinary infection, showed a similar association of dysmorphic kidneys, with the severe forms of VUR disorder in patients younger than 1 year.[23] In these infants, the proportions of boys and girls were similar (1:1.63), and diffuse abnormalities were four times more common than focal abnormalities. In children presenting after age 5 years, when girls predominated by 4:1, diffuse abnormalities also were seen, but the incidence of focal scarring had increased so that the proportions of children with diffuse and focal abnormalities were similar. These changing figures may represent acquired scarring or differential areas of growth within an abnormal kidney, or both.

Pathogenesis of Acquired Renal Scarring: Experimental Studies

Experimental studies have defined the factors that are important for acquired renal scarring: intrarenal reflux, urinary infection, and, less commonly, extreme urodynamic abnormalities.

Intrarenal Reflux

Intrarenal reflux, or pyelotubular backflow, is the retrograde passage of urine into the collecting ducts and nephrons. It has a segmental distribution, occurring predominantly at the renal poles. Its significance in the genesis of segmental scarring was first shown experimentally by Hodson and coworkers[128]; renal scars formed only in areas where intrarenal reflux was previously shown (Fig. 22-10). The same has been observed in clinical practice.[127]

Intrarenal reflux can occur only when there is a reversal of the normal antegrade dynamics within the upper urinary tract, such as occurs during the reflux event, when the upper tracts are exposed to high pressures generated during micturition. The direct transmission of bladder pressures to the renal pelvis, which occurs only in the presence of reflux, was shown in the pig model (see Fig. 22-3).[147] The intrarenal backflow occurs as an extension of the retrograde dynamics. The phenomenon exposes the renal tubules to abnormal pressures, to pressures of urine stored in the bladder, and provides a means for urinary pathogens to gain access to the renal substance.

The segmental distribution of intrarenal reflux is related to variation in renal papillary morphology. Fusion of renal lobules during embryologic development results in compound papillae. This process normally occurs in the poles of the kidney, whereas simple (single lobule) papillae are more frequent in the midzone. The morphology of the papillae correlates with the potential for intrarenal reflux. Compound papillae present flat or concave cribriform areas bearing open Bellini ducts allowing intrarenal reflux. Simple papillae present a

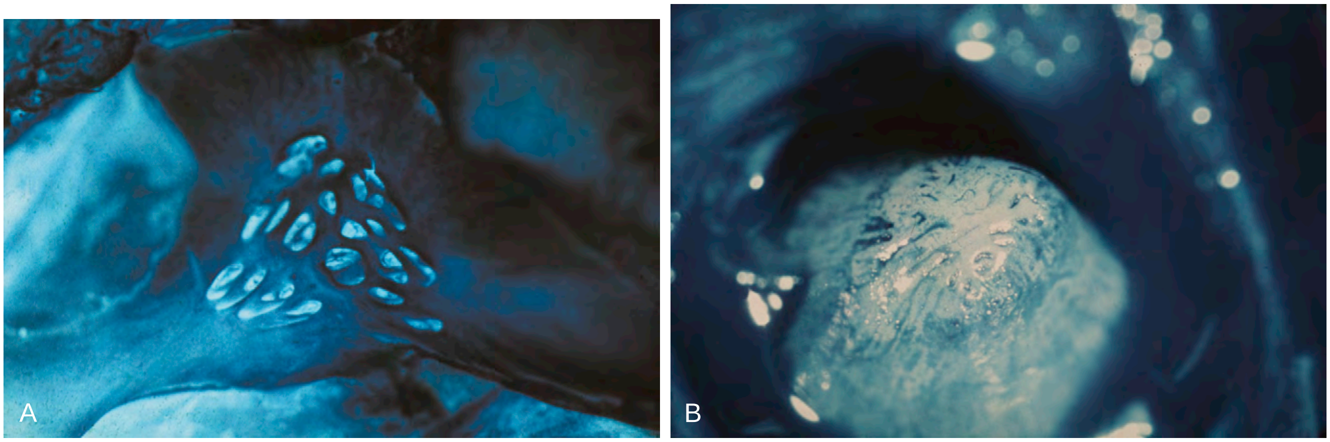


Figure 22-11 **A,** Compound papilla with gaping ductal openings present on a concave surface. **B,** Simple conical papilla with slitlike ductal openings. (From Ransley PG, Risdon RA. Reflux and renal scarring. *Br J Radiol Suppl.* 1978;14:1.)

convex surface with slitlike orifices that create a valvular mechanism preventing intrarenal reflux (Fig. 22-11). These observations were made in a pig model, which has the same multirenculate, multipapillate kidney similar to humans.[148]

The same variation in papillary morphology was found in human kidneys from infants and children.[149] Compound papillae of the type that allowed intrarenal reflux were present in 63% of kidneys and occurred predominantly at one pole or, less frequently, at both of the renal poles. That 27% of the kidneys had only simple papillae, which are not usually associated with intrarenal reflux, may explain in part why some children do not acquire renal scarring from infected VUR. Similar observations were made by Tamminen and Kaprio.[150]

Using the pig model with surgically induced VUR, Ransley and Risdon[126] showed that, without exception, scar formation in the presence of urinary infection occurred only in relation to refluxing papillae. The potential for intrarenal reflux is determined, however, by a combination of the shape of ductal openings and the surface architecture. Any physical distortion of the morphologic configuration, such as flattening of conical simple papillae, can turn a nonrefluxing ductal opening into one that allows intrarenal reflux. When voiding pressures and consequently intrapelvic pressures were increased in animals with VUR, by inducing a urethral constriction, the renal scarring was more extensive, and the proportion of refluxing to nonrefluxing papillae was greater.[126,128] In the extreme, when urinary outflow is severely impaired by an infravesical obstruction, there can be devastating effects from the combination of urinary infection and intrarenal reflux with profound renal scarring (Fig. 22-12).[128,151,152]

Urinary Infection

The pig model with unilateral VUR surgically induced early in life has shown that, in the absence of severely impaired urinary flow, renal scarring can occur only in combination with VUR and urinary infection, even when voiding pressures are increased by inducing a urethral constriction. In this unilateral model, the contralateral kidney, which was exposed to urinary infection but without reflux, did not develop scarring (see Fig. 22-12).[126]

After institution of urinary infection in the pig model with VUR, the pathogenesis of the renal scars typically showed a rapid progression from small discrete abscesses, reflecting individually affected tubules, to coalescent abscesses, or a confluent mass. Within 2 weeks, irreversible scarring was established, and by 3 weeks scar contraction could occur. The acute phase featured active interstitial inflammatory cell infiltration. By 2 weeks, the inflammatory cell infiltration was patchier, with lymphoid follicles evident, and active tubular destruction occurred with a variable amount of interstitial fibrosis (Fig. 22-13). The histopathology of established scars was indistinguishable from that found in clinical reflux nephropathy specimens.[126,153]

The effects of treatment showed that antimicrobial therapy instituted 1 week after infection, or during the early inflammatory phase, could limit the extent of scar formation. Residual pathology was present as fine linear scars (sometimes barely visible to the naked eye) extending through the cortex and marked by a small dimple on the renal surface (Fig. 22-14). Tubules were not evident within these linear fibrous streaks, and inflammation was minimal.[153,154] The effects of early treatment in confining scarring to a few affected tubules correlated with reversal of the corresponding scintigraphic abnormality seen on Tc^{99m} DMSA imaging (see Fig. 22-14).[154] These observations concur with clinical reports of improvement or reversal of the Tc^{99m} DMSA imaging abnormalities associated with acute pyelonephritis.[155,156] The experimental studies emphasize the importance of rapid treatment for acute

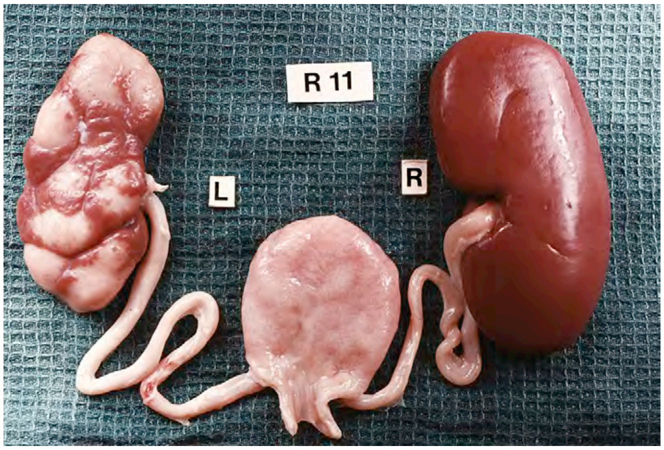


Figure 22-12 Extensive renal scarring acquired in the pig model with left-sided vesicoureteral reflux, urinary infection, and bladder outflow obstruction. Both ureters are dilated. The right kidney without vesicoureteral reflux remained normal.

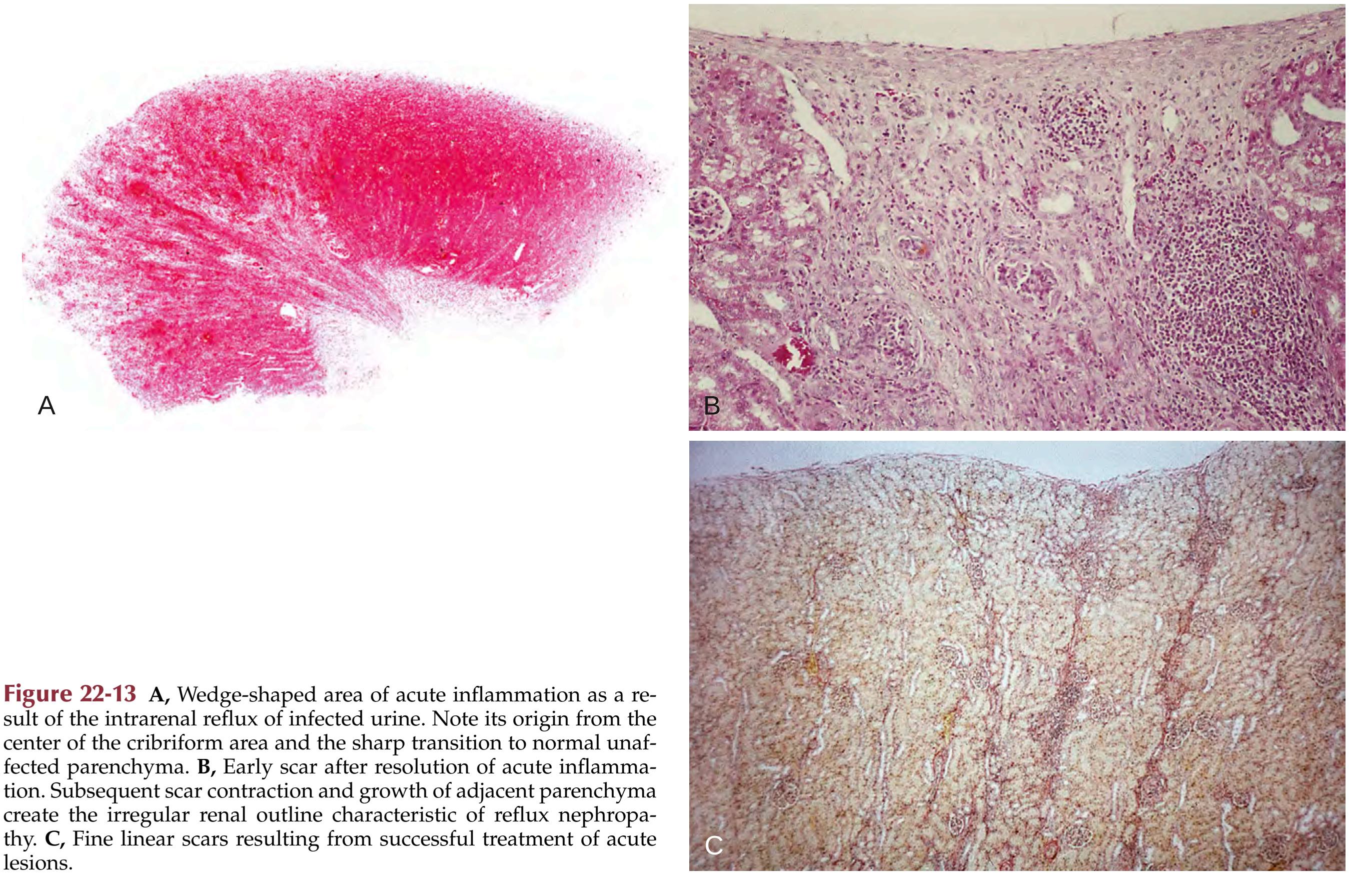


Figure 22-13 **A,** Wedge-shaped area of acute inflammation as a result of the intrarenal reflux of infected urine. Note its origin from the center of the cribriform area and the sharp transition to normal unaffected parenchyma. **B,** Early scar after resolution of acute inflammation. Subsequent scar contraction and growth of adjacent parenchyma create the irregular renal outline characteristic of reflux nephropathy. **C,** Fine linear scars resulting from successful treatment of acute lesions.

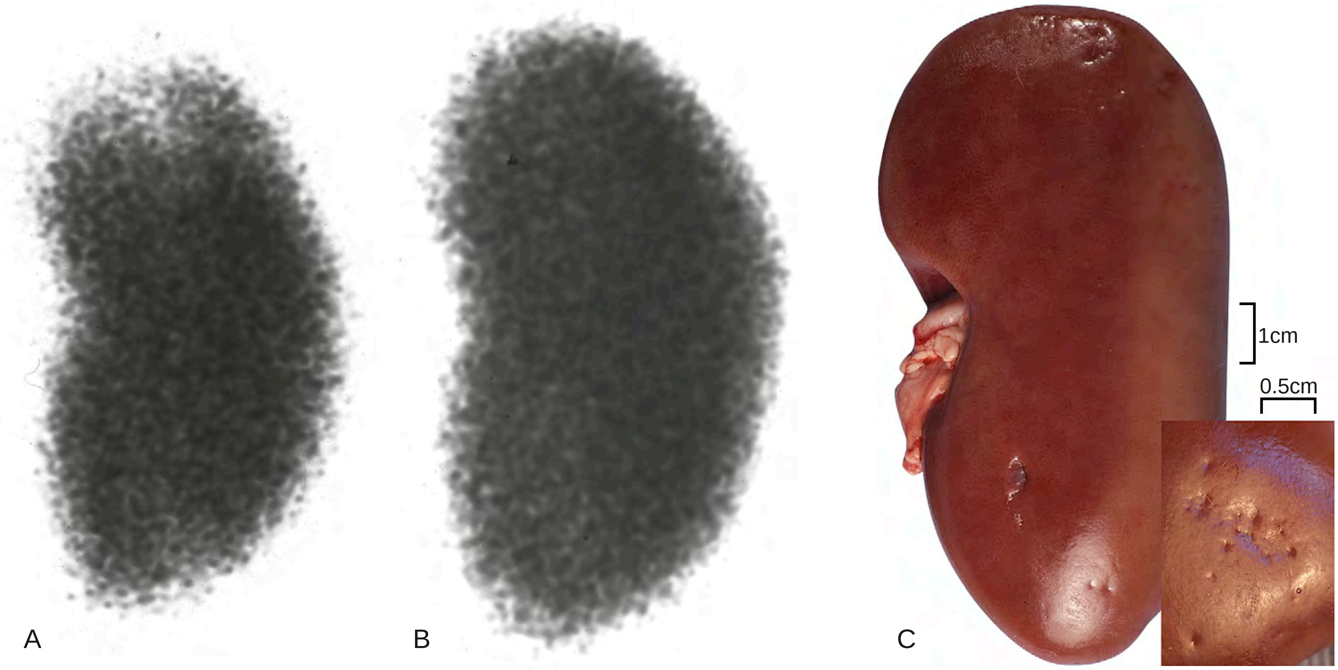


Figure 22-14 **A** and **B,** Tc^{99m} DMSA renal images show a minor lesion in early acute pyelonephritis in the pig **(A)** and resolution of the imaging abnormality after 3 weeks of treatment with antibacterial agents **(B). C,** Posterior surface of the kidney specimen corresponding to image **B,** showing the residual abnormality; *inset* shows "dimpled" scars. (Adapted from Risdon RA, Godley ML, Gordon I, et al. Renal pathology and the 99mTc-DMSA image before and after treatment of the evolving pyelonephritic scar: an experimental study. *J Urol.* 1994;152:1260.)

pyelonephritis in clinical practice to limit the damage of reflux nephropathy.

The rapid development of focal renal scarring after initiation of urinary infection has since been confirmed in an adult pig model with induced unilateral VUR.[157] The risk of acquired nephropathy from infected urine is the same in immature and adult pig kidneys. The same is true in humans because adult kidneys transplanted into children also develop focal scarring.[158,159] These findings emphasize the "big bang" nature of acquired scars, described by Ransley and Risdon.[126] In susceptible individuals, one episode of untreated urinary infection early in life is sufficient to establish scars, after which new scarring is rare.

The experimental studies using the pig provide a plausible explanation for the pathogenesis of acquired scarring that concurs with the clinical observations of new focal scarring observed in children with infected VUR. There is controversy, however, concerning the role of VUR in acute renal infection and pyelonephritis.

Acquired Pyelonephritis in the Absence of Vesicoureteral Reflux

The crucial role of VUR in the genesis of focal renal scarring is now challenged by reports of pyelonephritic lesions identified during or shortly after acute urinary tract infection without VUR shown by subsequent cystography.[133,160] A review by Rushton and Majd[161] revealed that 20% to 90% of infants and young children had renal abnormalities with Tc^{99m} DMSA imaging, but smaller proportions (20% to 30%) had coexistent VUR identified. In considering only the patients with acute changes on imaging, most (63% to 75%) did not have VUR identified. For interpretation, however, it is important to discriminate between new lesions and established scars. The presence of renal scarring in the absence of VUR is a well-recognized feature of the spontaneous resolution of VUR while renal scarring and a predisposition to urinary infection persist. Experimental studies have shown that although acute and established lesions can be distinguished on Tc^{99m} DMSA imaging, there are many exceptions.[130,134,162] There is a potential in the clinical setting for small, established scars or congenital lesions to be mistaken for acute pyelonephritis.

Reports of resolution or improvement of the acute imaging abnormalities have been noted in a substantial proportion of children, which substantiates the acute and often reversible nature of the associated underlying pathology.[155,156] These reports also noted, however, that when progression from "acute inflammatory lesions" to established "scarring" did occur, it was independent of whether VUR was identified.

Alternative explanations for the genesis of "nonreflux" pyelonephritis are (1) hematogenous spread of infection, (2) ascending pyelonephritis in the absence of reflux, and (3) transient VUR during the acute infection. The focal nature of the pyelonephritis, the same as in reflux nephropathy, makes it unlikely that hematogenous spread is a dominant mechanism, and instead implies that intrarenal reflux has a major role. Likewise, ascending pyelonephritis in the absence of VUR, evidenced in the monkey[163] and attributed to paralysis and dilation of the ureter by P-fimbriated *E. coli,* may operate clinically in some instances.

The failure to detect reflux on a late investigation is not evidence for the absence at some earlier and critical time. Reports document the transient and elusive nature of reflux after pyelonephritis. A second investigation may be required when isotope cystography is recommended.[164-167] The fallibility of detecting reflux is compounded further because cystography cannot be performed during an acute phase of urinary infection. Only a brief episode of VUR and intrarenal reflux may be necessary for a parenchymal inoculation of bacteria sufficient to induce changes on Tc^{99m} DMSA scintigraphy, which is highly sensitive in detecting the initial stages of pyelonephritis, when there is only limited pathologic involvement (see Figs. 22-9 and 22-14).[134] The high resolution or improvement rate (83%) for acute pyelonephritis noted in a study by Rosenberg and colleagues[156] implies limited tubular involvement. A transient reflux event induced by the infective insult is the most plausible pathogenic mechanism. The inflammatory responses at the UVJ, abnormal urodynamics, and endotoxin from P-fimbriated *E. coli* that can paralyze the ureter are potential factors facilitating the reflux event.

Sterile Vesicoureteral Reflux and Acquired Renal Scarring

Sterile VUR in itself does not cause renal scars. In weanling piglets with VUR, renal scarring was induced only when urinary infection was present.[126] In neonatal lambs,[168] in dogs,[169] and in monkeys,[170] there was no evidence that reflux itself induced a scarring mechanism. In clinical practice, evidence is largely circumstantial, but conservative management of patients with VUR is founded on the recognition that scarring does not occur when sterile urine is maintained with antibacterial prophylaxis.[73]

The subject of sterile scars was contentious for many years after experimental observations by Hodson and coworkers[128] associating the intrarenal reflux of sterile urine with renal scarring. It is now recognized from studies in the pig by Ransley and colleagues,[151] Jorgensen and colleagues,[171] and Heptinstall and Hodson[172] that sterile segmental scarring can be acquired only in extreme hydrodynamic conditions amounting to obstruction, when VUR is combined with severe bladder outflow obstruction resulting in retention of urine, upper tract dilation, and *sustained* high pressures within the urinary tract. Mendoza and Roberts[173] made similar observations in monkeys, and found that parenchymal damage occurred only when the urodynamic abnormality was sufficient to cause a delay in renal excretion rate (i.e., the presence of obstruction).

The urodynamic features associated with sterile scars in the pig were prolonged periods of phasic high pressures repeated frequently with persistent attempts at voiding (Fig. 22-15). They were analogous to some of the more severe urodynamic abnormalities encountered in newborn infants with posterior urethral valves before resection or in the obstructed neuropathic bladder. There were variable degrees of urinary tract dilation, and scarring sometimes involved numerous papillae owing to distortion of the papillary morphology and recruitment of previously nonrefluxing papillae, as described earlier. Scar formation resulted from tubular interstitial damage with rapid progression to interstitial collagen deposition, but without the cellular inflammatory response.[151]

Pathogenic Mechanisms of Renal Scarring

The tissue fibrosis that constitutes the segmental scars occurs as a function of tissue repair in response to cell damage. Fibrosis most likely results from increased cell matrix synthesis and deposition together with a decrease in degradation. Various mediators are involved, principally cytokines, growth factors, and angiotensin II. The subject generally is of considerable current interest and has been reviewed.[122,174,175] Although molecular studies are rarely directed specifically at segmental renal scarring, they extend to tubulointerstitial fibrosis and obstructive nephropathy, and there are mechanisms in common with fibrosis in other systems.

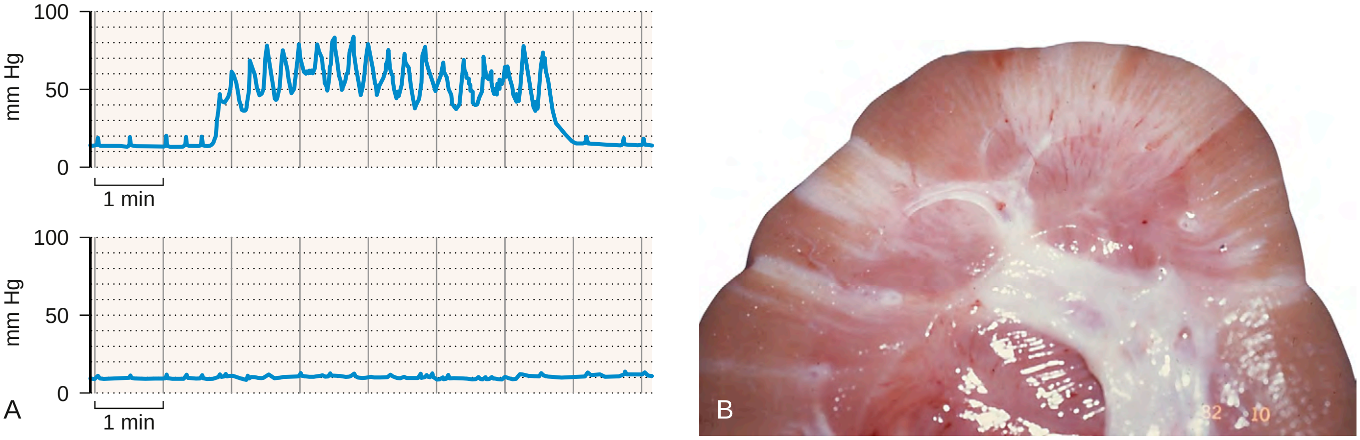


Figure 22-15 **A,** Urodynamic trace of a bladder with severely impaired urinary outflow and upper tract dilation in a pig with vesicoureteral reflux. This shows only one of a series of prolonged contractions with poor urine outflow, which was repeated frequently (*upper trace* shows intravesical pressure; *lower trace* shows abdominal pressure). **B,** Sterile segmental renal scarring from the same pig 2 weeks later.

Damage to tubular epithelial cells is the initiating process that activates a cascade of mediators. For the most part, the processes leading to tubular cell damage have been considered in relation to acute pyelonephritis; this subject has been reviewed by Roberts[176] and by Svanborg and coworkers.[97] There is accumulating evidence implicating ischemia and reperfusion damage with release of superoxide, which together with other free radicals of oxygen destroys lipid cell membranes.[177] A focal decrease in renal blood flow at sites of acute pyelonephritis was reported after experiments in pigs[178] and in rabbits.[179] Kaack and associates[180] provided indirect evidence for ischemia by showing transiently elevated renal vein renin during the early inflammatory phase of pyelonephritis in a primate model. Renal ischemia may result from compression of vasa recta and peritubular capillaries by edema,[181] or from obstruction of the capillary vasculature with platelet and granulocyte aggregation.[182] Superoxide and other free radicals of oxygen are produced by the respiratory burst from neutrophilic leukocytes during bacterial phagocytosis and by metabolism of the products of anaerobic metabolism of adenosine triphosphate.

Experimental evidence supporting reperfusion injury has shown that damage inflicted during acute pyelonephritis can be limited by modulating the chemical mediators and the pool of free radicals. This modulation has been achieved by delivery of exogenous superoxide dismutase[183]; by complement depletion,[184] which modulates the inflammatory response; or by pretreatment with the xanthine oxidase inhibitor allopurinol, which decreases free radical production from anaerobic metabolism.[185]

Genetic factors may be associated with the risk of renal scarring secondary to VUR. There has been considerable investigation of angiotensin-converting enzyme gene polymorphisms in this context, but there is no consensus of opinion.[186,187] More positively, more recent reports suggest that specific polymorphism of the gene governing transforming growth factor-β, a proinflammatory and fibrogenetic cytokine, may be involved in presenting a higher risk of reflux nephropathy.[188] Transforming growth factor-β has been found as an abnormal urinary protein in children with a first urinary infection. It was present more frequently and at higher concentrations in children who had normal kidneys on subsequent Tc^{99m} DMSA scan than in children with renal scarring, suggesting a regulatory role in fibrogenesis affecting the outcome of pyelonephritis.[189]

Because the nature of the host response to infection may be the important factor in determining whether or not scar formation occurs, susceptibility to scarring also might be genetically determined. Neutrophils attracted by mucosal inflammation are an essential part of the bacterial clearance mechanism, but must migrate between the renal tubular cells to gain access to the bacteria within the tubular lumen. With a chemokine receptor (CXCR1) deficiency, this cell migration is prevented so that there is a buildup of leukocytes on the outside of the tubule, which die and release massive quantities of superoxide and cytokines that result in the death of tubular cells rather than the bacteria.[190,191]

Experimental Fetal Nephropathy

The congenital type of "sterile" nephropathy is significantly associated with severely dilated upper tracts that are predominant in boys. Most male and female infants with VUR detected after prenatal hydronephrosis have normal kidneys, testifying to a benign influence of fetal VUR.[32] The pathogenesis of the congenital nephropathy and upper urinary tract abnormality is unknown; however, a primary embryologic malformation is likely to be the dominant cause as discussed earlier. The impact of abnormal dynamics in the fetal urinary tract has yet to be fully evaluated, but cannot be excluded as a contributory factor in some instances of renal maldifferentiation. It is common for kidneys of children with posterior urethral valves or other forms of infravesical obstruction to show evidence for dysplasia or hypoplasia, the same as in some kidneys from children with VUR. Urinary outflow impairment can cause renal dysplasia in fetal sheep,[125,192,193] and similar mechanisms may operate in utero in humans in the event of impaired urinary outflow. Transient urethral anomalies can occur in boys and result in severe outflow obstruction.[194,195]

A series of experiments in fetal sheep have attempted to emulate possible in utero events that may account for congenital urinary tract pathology. Gobet and colleagues[196] postulated that the timing or coordination of developmental events related to structures specific to the male lower urinary tract may be crucial features in determining whether impaired urinary outflow occurs. This postulation followed their observations that hydroureteronephrosis and associated renal pathology occurred in males, but not females, after occlusion of the urachus during gestation. VUR was not noted to occur as a consequence, which suggests that it is not an inevitable outcome of an impediment to urinary outflow. In male animals, the renal morphology at birth showed distended calyces, cortical thinning, and medullary loss associated with hydronephrosis. These features were more pronounced after fetal VUR was experimentally induced in some male animals, exposing the kidneys directly to abnormalities in lower tract function. Renal dysplasia was never seen. Results reporting increased kidney weight and increased total collagen deposition as a consequence of reflux are difficult to interpret because it is unknown whether the kidneys were larger as a result of increased water content or increased protein mass. In female animals without marked hydronephrosis, despite the urachal ligation and urethral ring, an induced VUR had no effect.[197]

A better understanding of the precise origin and nature of urodynamic abnormalities occurring in utero is required before this model can be compared with a possible human situation. Whatever the urodynamic abnormalities that existed in utero in the male sheep model, they did not result in the spontaneous occurrence of VUR.

There is indirect evidence from fetal sheep with bladder outflow impairment that parenchymal maldevelopment may result from induced VUR and obstruction in utero. In humans, the association of grossly distended ureters, renal dysplasia, and VUR is more likely to reflect a common developmental error of the ureteral bud, as suggested by Mackie and Stephens.[59] Undoubtedly, there are other mechanisms still unknown, and there is accumulating evidence for a genetic basis.

Sterile Vesicoureteral Reflux and Renal Growth and Function

VUR does not affect renal growth or exert any significant pathologic effect on renal function. Small changes in functional parameters have been noted in the experimental setting, but their biologic and pathologic significance cannot be established. Clinical reports of a detrimental effect of VUR have arisen from a failure to account for the compounding factors of renal scarring and urinary infection. In studies examining the independent effect of VUR, there were no adverse effects of VUR on renal growth[198-200] or glomerular function.[201] Reports of elevated excretion of markers for tubular damage (e.g., NAG) with VUR have similarly been confounded by not discriminating between the presence of renal scarring and urinary infection.

In controlled experiments with minipigs monitored for 6 months having either a solitary kidney undergoing growth and compensatory growth or paired kidneys and unilateral reflux, sterile VUR did not affect renal growth, glomerular filtration rate, or relative uptake of Tc^{99m} DMSA. The outcome was the same even in the presence of elevated bladder pressures induced by a urethral constriction.[202,203] In the solitary kidney model, urinary concentrating ability was significantly diminished by reflux.[202] The diminution was small, however, and the levels remained within a clinically normal range. Similarly, impaired concentrating ability has been reported in children with VUR in the absence of renal scarring,[204] although the outcome may have been influenced by preexisting urinary infection, which can affect concentrating ability for 12 weeks.[205]

A subsequent pig study of the effects of sterile unilateral VUR, which incorporated computed tomography, contrast-enhanced magnetic resonance imaging, relative uptake of Tc^{99m} DMSA, and measurement of regional blood flow, found no significant effects on renal growth and function. Histologic examination showed rare foci of interstitial inflammation and fibrosis after 1 year in all refluxing kidneys and in one contralateral nonrefluxing kidney. There were no sham control animals with paired nonrefluxing kidneys for comparison.[206]

Evidence that VUR affects renal blood flow is inconsistent, but overall suggests that an effect cannot be disregarded. A diminution of effective renal blood flow was reported from one study of children with VUR and no renal scarring.[207] In the experimental setting, an impact on effective renal blood flow was noted in monkeys only when there was "functional urinary flow impairment."[173] Similar results were found in a pig model by Helin and associates,[208] and are consistent with observations from Heptinstall and Hodson[172] of perivascular fibrosis in a proportion of pigs with elevated intravesical pressures and sterile reflux. Subtle changes in blood flow have been noted in other circumstances. A decrease in renal blood flow during voiding, greater than the decrease that can occur normally, was noted in dogs with VUR, and there was a diminution of blood flow when intrarenal reflux was induced by retrograde perfusion in pigs.[209,210] Experiments examining the intrarenal blood flow distribution in pigs with the use of radioactive microspheres showed VUR did not influence whole kidney blood flow, but did affect the cortical distribution in certain regions.[211]

The significance of the physiologic effects of VUR in relation to the clinical disorder has not been established. The sensitivity of homeostasis is such that abnormal events are unlikely to pass without exciting perturbations, but these may not indicate or represent a pathologic process.

Summary

Salient points regarding congenital reflux nephropathy are as follows:

- Congenital reflux nephropathy is part of an embryologic field defect.
- Intrarenal reflux of infected urine through compound papillae is central to the acquired scarring process.
- Sterile urine causes scarring only with extreme lower urinary tract obstruction, and when *sustained* high pressures are transmitted to the kidney in the presence of reflux.
- The fetal kidney is exquisitely sensitive to abnormal dynamics. This may be a nongenetic mechanism for congenital nephropathy.
- Early treatment of infected renal parenchyma may limit or prevent scar formation.

SUMMARY

VUR is a harmless dynamic event that possibly occurs in large numbers of children without ever being recognized, particularly in boys. It is the product of ureterotrigonal dysfunction or maldifferentiation. It is significant as a component in clinical disorders only when associated with other urinary tract problems. It can be one component in a primary maldevelopment of the urinary tract that predominantly affects boys and may include nephropathy. The effect of VUR is to expose the kidney to intrarenal reflux, which extends lower tract dynamics and any urinary pathogens into the renal tubules to initiate acquired renal scarring. There may be teratogenic or genetic origins to explain a predisposition for urinary infection and abnormal lower tract function, the interaction of which can turn a harmless event into a clinical disorder with pathophysiologic consequences that predominantly affects girls.

Salient points regarding VUR are as follows:

- Severe bilateral reflux nephropathy leading to chronic renal failure occurs predominantly in boys, and the nephropathy is congenital in origin.
- Management strategies must be sensitive to the potential for bladder dysfunction in this group.
- Girls with reflux have predominantly normal kidneys at birth.
- Girls present with urinary infection or bladder dysfunction or both, which may be the causative factors generating reflux.
- Renal parenchymal involvement requires the combination of abnormal dynamics, compound papillae, and urinary infection with organisms carrying adhesion molecules.
- The evolution of a scar from such circumstances may depend on delay in treatment or genetic factors controlling host response to bacterial infection at a cellular level.
- There is little evidence that control of the reflux event itself has a significant impact on the renal outcome.

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For complete list of references log onto www.expertconsult.com

CHAPTER 23

THE DIAGNOSIS AND MEDICAL MANAGEMENT OF PRIMARY VESICOURETERAL REFLUX

Saul P. Greenfield and Julian Wan

Vesicoureteral reflux (VUR) is one of the most important diseases of childhood. If unrecognized and inadequately treated, it can lead to pyelonephritis, renal scarring, hypertension, and renal insufficiency. Reflux is defined as retrograde flow of urine from the bladder into the ureter. *Primary reflux* refers to reflux that is due to an intrinsic defect within the ureterovesical junction. *Secondary reflux* is the term applied to reflux that is the result of another pathology; reflux associated with congenital bladder outlet obstruction or abnormally elevated intravesical pressure secondary to neurogenic bladder dysfunction would be termed secondary reflux. In this chapter, the general use of the term *reflux* refers to primary reflux.

Identification of reflux usually occurs as part of an evaluation of a child who had a culture-proven urinary tract infection (UTI). The mainstay of this evaluation is a voiding cystourethrogram (VCUG). Medical management is based on the observation that VUR in most affected children spontaneously resolves with growth. The likelihood of resolution is inversely related to the severity of the reflux. Children with lower grades of reflux are more likely to improve over time.

These concepts have formed the foundation of any conservative management plan for the past 50 years. Many controversies exist regarding diagnosis and management (Table 23-1): Are there less invasive alternatives to the VCUG? Among children with UTI, can the indications of evaluation for reflux be refined? Who else should be imaged for reflux? How can we better predict whose reflux will resolve spontaneously and whose will not? When should a conservative approach be abandoned in favor of surgery? This chapter discusses these questions and gives one perspective on the diagnosis and nonoperative management of reflux.

DIAGNOSIS

Methods of Imaging

Voiding Cystourethrogram

Retrograde imaging of the bladder and urethra was first described in 1905. By the 1930s, the modern combination of retrograde contrast instillation, fluoroscopy, and observation during filling and micturition was developed.[1] The VCUG is the principal method of assessing the lower urinary tract in children.[2] The VCUG can quantify reflux in a more accurate and prognostically useful way. The most commonly accepted classification system is the International Reflux Study (IRS) group method, which separates reflux into five grades (Figs. 23-1 and 23-2).[3] In addition to visualizing the reflux, the VCUG images the urethra and bladder. Other conditions that can predispose to UTI, such as diverticula, posterior urethral valves, neurogenic dysfunction (i.e., trabeculated bladder), urethral strictures, and ureteroceles, all can be detected. The plain film, which is routinely taken before contrast instillation, also can identify incidental findings, such as stones, vertebral anomalies, and constipation.

VCUG images allow consistent interpretation. There is near-perfect agreement in their interpretation between independent groups of experienced radiologists.[4] Comparison between digital images versus traditional hard copy found no statistical difference.[5]

The VCUG requires catheterization and uses ionizing radiation near the gonads. The catheter may increase urethral resistance, increasing the voiding pressure. This pressure increase has been theorized to exaggerate the degree of reflux.[6] Some clinicians argue that the VCUG is nonphysiologic and not representative of normal voiding. The study is done in a supine position, and catheter placement can be traumatic leading to higher than normal bladder volumes. To mitigate these concerns, the use of lidocaine jelly lubrication and mild sedatives that do not affect bladder activity has been advocated.[7] Oral midazolam has been used successfully with 60% of the children not recalling the study.[8] Another option is to reduce the frequency of imaging. Thompson and colleagues[9] proposed that the current American Urological Association guidelines for mild reflux can be extended to every other year and every 3 years for moderate or severe reflux. There are also technical concerns that cases of reflux could be missed because images are captured only at fixed points. Short-duration episodes, which are nonetheless clinically significant, could be missed. For all of these reasons, alternative methods of evaluation have been sought.

Radionuclide Studies

The practical application of radioisotopes in pediatric urology was limited until the 1960s. The invention of the gamma scintillation camera and the development of technetium 99m (Tc^{99m})–based tracers led to the expanded use of radionuclide imaging.[10] Among the better known tracers are diethylenetriamine penta-acetic acid (DTPA), dimercaptosuccinic acid (DMSA), and mercaptoacetyltriglycine (MAG3).

Because VUR can lead to renal damage; assessment of renal function is important. Renal scanning using Tc^{99m}-DMSA is the preferred method of assessing growth and development. Tc^{99m}-DMSA concentrates in the renocorticotubular cells. Irregularities in the contour, representing scars, are sharply delineated. In 1989, Goldraich and associates[11] showed Tc^{99m}-DMSA scanning was more accurate than intravenous pyelography (IVP) in determining the presence of renal scarring. Rushton and coworkers[12] showed that Tc^{99m}-DMSA scanning identified areas of scarring and sites of acute pyelonephritis, establishing that acute pyelonephritis can lead to scarring. The correlation between Tc^{99m}-DMSA defects and pyelonephritic lesions (Fig. 23-3) was supported further in an animal study by Risdon and associates,[13] who showed the defect in the image and histologic changes in piglet kidneys with reflux and pyelonephritis. In the 1990s, improvements in ultrasonography led to the conjecture that it could supplant Tc^{99m}-DMSA as a means of assessing renal damage. Although ultrasound is useful in detecting large diffuse scarring, smaller focal scars are missed.[12]

The nuclear cystogram, or isotope cystogram, is the radionuclide analogue of the VCUG using a tracer such as

Tc^{99m}-DTPA (Fig. 23-4). This test offers several advantages over the VCUG, including continuous imaging and less radiation.[13,14] These advantages are offset by a cruder grading system. The degrees of reflux are subjectively reported as "mild," "moderate," or "severe." The urethra cannot be imaged, and incidental findings in the bladder, pelvis, abdomen, or spine cannot be detected. Grade I reflux can be obscured by the bladder image. Some authors routinely use the VCUG as the initial study to identify reflux, and then use the nuclear cystogram for subsequent follow-up studies.[15,16] This method reduces overall radiation exposure, but precludes the comparison of initial and subsequent reflux grades.

Table 23-1 Considerations of Nonoperative Management of Vesicoureteral Reflux

Are there alternatives to VCUG as an imaging modality for VUR that are less invasive or more efficacious or both?
In addition to children with UTI, who else should be imaged for VUR?
In families with children with VUR, should other siblings be imaged for VUR?
In addition to age and severity, what factors seem to affect the rate of resolution?
How can we better predict which children will resolve VUR spontaneously and which children will not?
When should a conservative approach be abandoned in favor of surgery?
What should be done about older children with VUR?
Is it practical to follow children with VUR over many years?

UTI, urinary tract infection; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux.

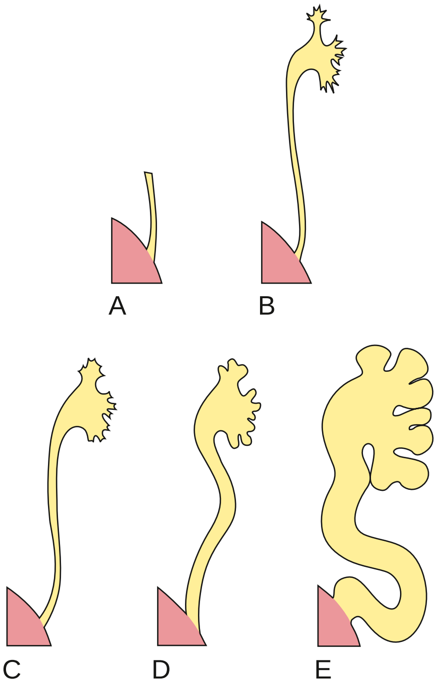

Figure 23-1 International Reflux Study grading system for vesicoureteral reflux. **A,** Grade I—reflux into the distal ureter only. **B,** Grade II—reflux into the renal collecting system without distention of the calyces. **C,** Grade III—reflux into the renal collecting system causing mild distention of the collecting system and minimal ureteral tortuosity. **D,** Grade IV—reflux into the renal collecting system with moderate distention and ureteral tortuosity. **E,** Grade V—severe reflux into renal collecting system with severe distention and ureteral tortuosity. (From Hilton SvW. The child with a urinary tract infection. In: Hilton SvW, Edwards DK, eds. *Practical Pediatric Radiology.* 2nd ed. Philadelphia: Saunders; 1994, p 501.)

Nasrallah and colleagues[17] tried to improve nuclear cystogram accuracy and consistency by calculating the amount of tracer infused depending on the bladder volume and the amount of urine refluxed. Others have tried to eliminate the need to catheterize the child by introducing the tracer intravenously and letting it accumulate in the bladder naturally (Fig. 23-5). This indirect form of radionuclide cystography has a 10% false-negative rate and a 15% false-positive rate.[18] De Sadeleer and coworkers[19] compared indirect radionuclide cystogram with the VCUG and nuclear cystogram, and found that the indirect radionuclide cystogram had more than double the number of false-negative results. Indirect radionuclide cystography requires a cooperative patient who can remain still during the study and who can void on request. More recent studies have found better concordance between the VCUG and nuclear cystogram. Rather than being viewed as rivals, the two studies should be seen as complementary; the initial screening for VUR, particularly if no urethral or bladder abnormality is suspected, could be done by the nuclear cystogram.[20]

Ultrasonography

The complete evaluation of a child with a UTI requires a lower and an upper tract study.[16,20-23] Ultrasonography of the kidneys and bladder is an excellent complement to the VCUG. Advances in resolution and clarity led to the hope that ultrasonography may be able to identify reflux independently

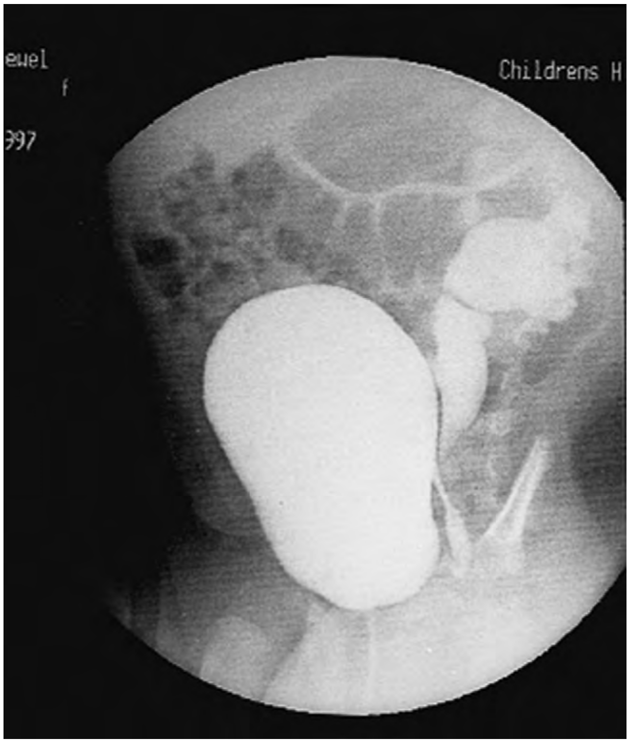

Figure 23-2 Voiding cystourethrogram shows grade IV reflux into the left kidney.

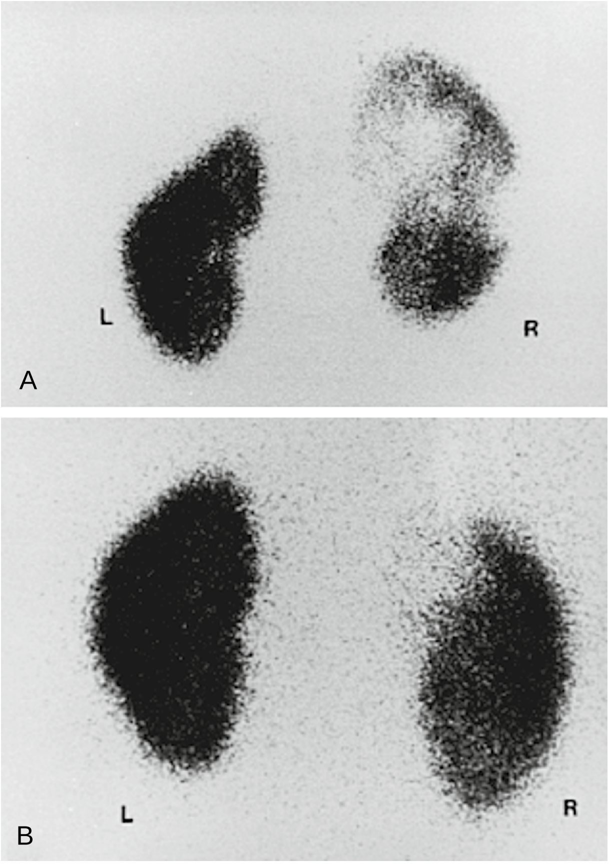

Figure 23-3 **A,** Renal scan of patient with acute pyelonephritis at time of illness shows several photopenic regions in right kidney. The left kidney is normal. **B,** Subsequent delayed scan shows persistence of photopenic region. This area is most likely at risk to develop a renal scar. (From Hilton SvW. The child with a urinary tract infection. In: Hilton SvW, Edwards DK, eds. *Practical Pediatric Radiology.* 2nd ed. Philadelphia: Saunders; 1994, p 522.)

without ionizing radiation and urethral catheterization.[24] In 1977, Kuhns and associates[25] noted that children with VCUG-proven reflux lacked ureteral jets. They theorized that the presence of jets may be a strong negative predictor of reflux. Renal dilation before or after voiding has been observed with reflux.[26-28] In 1993, Blane and colleagues[29] convincingly showed that ultrasonography was not a reliable method of detecting reflux. Of the 986 kidneys evaluated, 28% were found to have reflux on VCUG. Of these 272 kidneys, 74% had a normal ultrasound without evidence of ureteral or renal pelvic dilation. All grades of reflux were missed on ultrasound, including more than 25% of kidneys with grade III or higher. A subsequent study by DiPietro and coworkers[30] confirmed the poor correlation between ultrasound and reflux. Of children age 5 years or older with VCUG-proven reflux, 29% had a normal ultrasound. Conventional ultrasound cannot be used to detect VUR.

Reported by Salih and associates in 1994,[31] color Doppler ultrasound technology was applied to the ureterovesical junction to image the directional flow of urine.[31] In this initial study, a 90% correlation between the VCUG and color Doppler ultrasound was noted for grades I and II, and a 100% correlation was noted for grade III. The false-positive rate was 20%. This promising technique has several limitations. The patient must be cooperative because motion artifact degrades the quality of the images, and the severity of reflux cannot be graded.

Bladder urine can be made echogenic to make it easier to visualize on ultrasound. Urine can be agitated to create microscopic bubbles, or an echogenic substance can be introduced. In 1990, Coulden and colleagues,[32] noting that agitated saline is used during echocardiography to help identify septal defects, suggested that a similar technique be tried. Hanbury and coworkers[33] showed that reflux could be effectively detected by this method with 100% sensitivity in identifying grades III and IV reflux. The false-positive rate was high, with only 60% of ureters identified as having reflux being confirmed on the VCUG. In a refinement of the concept, Atala and associates[34] in 1998 instilled sonicated albumin. The albumin was more echogenic, but there remained a high

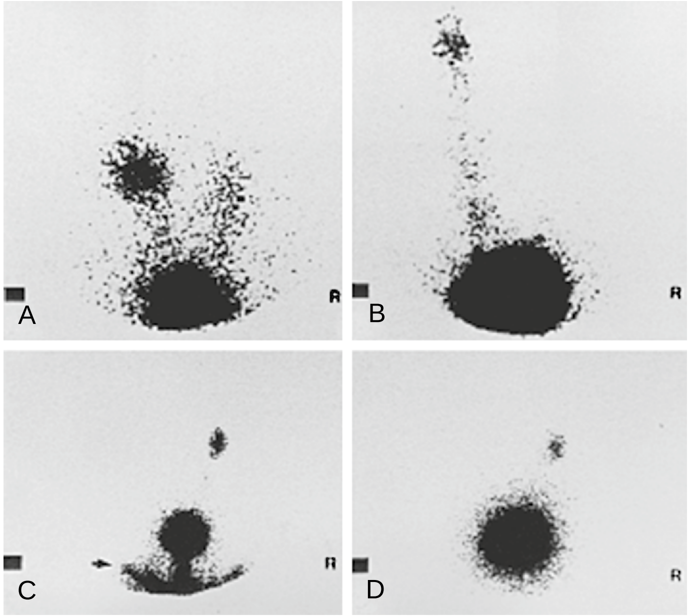

Figure 23-4 Four patients with vesicoureteral reflux (VUR) on direct nuclear cystography. **A,** Bilateral VUR, left more severe than right. **B,** Right-sided VUR only. **C,** Left-sided VUR. *Arrow* points to gathering of tracer in the patient's diaper. **D,** Right-sided VUR. (From Hilton SvW. The child with a urinary tract infection. In: Hilton SvW, Edwards DK, eds. *Practical Pediatric Radiology.* 2nd ed. Philadelphia: Saunders; 1994, p 519.)

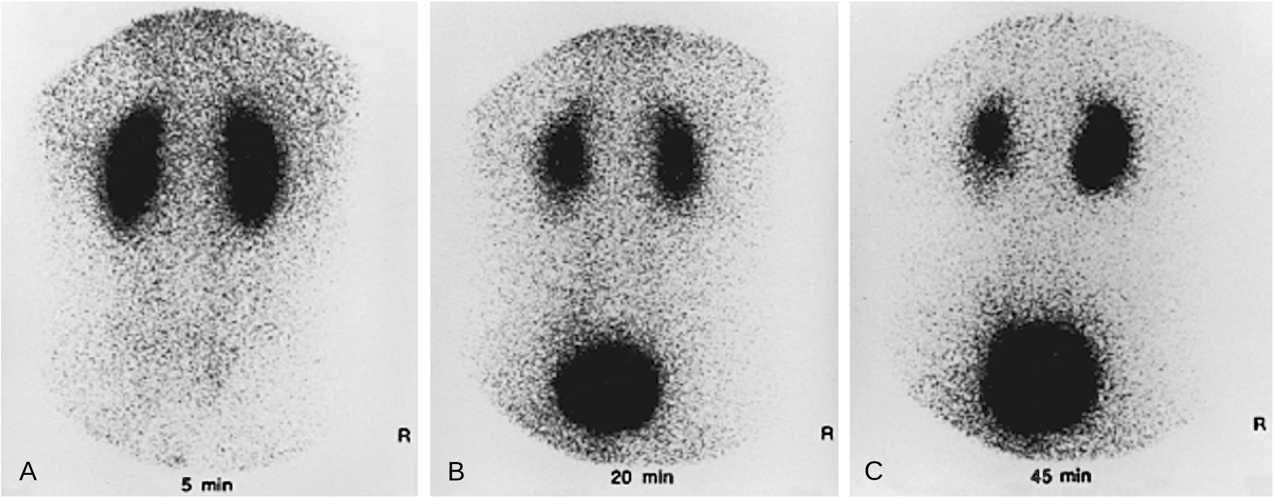

Figure 23-5 Indirect nuclear cystography. **A,** Posterior image taken at 5 minutes. Note tracer only in kidneys. **B,** Image at 20 minutes. Note tracer accumulating in bladder. **C,** Image at 45 minutes. An increase in activity is noted in the right renal pelvis, and a decrease in activity is noted in the left renal pelvis. This shows right VUR to the level of the kidney. (From Hilton SvW. The child with a urinary tract infection. In: Hilton SvW, Edwards DK, eds. *Practical Pediatric Radiology*. 2nd ed. Philadelphia: Saunders; 1994, p 520.)

false-negative rate: it missed 30% of patients with reflux. This technique requires that the patient be catheterized, and it cannot image the urethra. A contrast-enhancing suspension based on galactose (Levovist) has been introduced, but for now this novel concept is not yet practical.[35,36]

Magnetic Resonance Voiding Cystography

Magnetic resonance imaging (MRI) is appealing as a method of detecting of VUR: There is no ionizing radiation, anatomic detail is excellent, and IRS grading is possible. MRI also offers the ability to assess the kidneys for anomalies and reflux nephropathy. Rodriguez and colleagues[37] first noted that MRI using instilled gadolinium had comparable results. There are limitations, however: Images are obtained only before and immediately after voiding, young patients require sedation, and the required long scan time can underestimate or miss VUR. These limitations may be overcome by future advances.

PIC Cystography

When a VCUG does not show VUR in children who have recurrent febrile UTIs, management has been controversial. One idea advanced was that VUR may be “occult” and missed by the VCUG. It was suggested that directly instilling contrast material at the orifices while under anesthesia would unmask the “occult” VUR; this concept is known as a PIC cystogram (PIC for positioning the instillation of contrast). In 2003, Rubenstein and colleagues[38] first described the procedure and found good concordance with a control group with a known history of VUR.[39] There was 100% sensitivity in detecting VUR already known by standard VCUG. There was also 87% specificity in showing VUR in five ureters not previously known to have VUR with an overall accuracy of 91%. A multi-institutional report by Edmondson and coworkers[40] showed that the PIC cystogram detects “occult” VUR in about 80% of children with febrile UTI who have normal standard VCUGs. One question that lingers over this novel technique is whether the instillation pressure of 1000 mm H_2O suggests that the children affected by “occult” VUR may actually have an “occult” voiding dysfunction.

Table 23-2 **Potential Vesicoureteral Reflux Marker Molecules**

Serum endothelium leukocyte adhesion molecule-1 (ELAM-1)
Urinary retinol-binding protein
Urinary β-*N*-acetylhexosaminidase
Urinary *N*-acetyl-D-glucosaminidase (NAG)
Urinary interleukins (IL-8, IL-6)
Urinary Tamm-Horsfall protein (THP)
Urinary β_2-microglobulin

Nonimaging Modalities of Diagnosis and Evaluation

Are there serum or urine markers that could identify children with reflux? Measured levels of microproteinuria, urine retinol-binding protein, urinary prostaglandin E_2, urinary β_2-microglobulin, Tamm-Horsfall protein, β-*N*-acetylhexosaminidase, *N*-acetyl-D-glucosaminidase (NAG), urinary interleukin levels, procalcitonin, and serum endothelium leukocyte adhesion molecule-1 (ELAM-1) have been shown to be elevated in patients with reflux as opposed to controls.[41-51] Although these methods can neither localize the kidney affected by reflux nor assess the grade, they offer the potential of rapid screening (Table 23-2). They all showed good sensitivity, but poor specificity, being equally reactive with inflammation and VUR. Leroy and associates[46] found that a high serum procalcitonin level predicted VUR with a sensitivity of 80%, but with a specificity of only 44%. Markers may be useful someday, but currently they lack practical utility.

Who Should Be Imaged for Reflux

The prevalence of reflux in asymptomatic children with no history of culture-proven UTI is less than 2%. Ransley[52] found a 1.3% rate in asymptomatic and otherwise normal children. Individuals who present with voiding dysfunction and no history of UTI have a higher prevalence of reflux. Cutler and colleagues[53] studied children with enuresis and found reflux in 15%. In a 1991 study, 16% of children with nocturnal enuresis and no history of UTI were found to have reflux, including some with grades III and IV.[54] Among children with culture-proven UTI, the prevalence increases significantly to about 30% to 40%.[55,56] The consensus among contemporary pediatric studies is that children who have a culture-proven UTI should be evaluated. Gonzales and Roth,[16] Elder,[21] and Travis and Brouhard,[23] in their chapters on pediatric UTI, conclude that the prevalence of reflux is sufficiently high to warrant investigation with imaging studies. Beyond this general recommendation, however, there is controversy. The points of contention revolve around the pathophysiology and epidemiology of reflux nephropathy and the natural history of UTI and asymptomatic bacteriuria in children.

When reviewing these various positions, practical considerations must be kept in mind. In an ideal situation, all patients would be compliant, all infections would be brought to the attention of a physician, and all patients would receive appropriate imaging. In reality, many patients do not follow-up or never are evaluated at all.[56] Cohen and associates[57] in 2005 reported that less than half of infants younger than 1 year of age in a statewide study who were diagnosed with a UTI received the recommended medical care, and there was a marked difference in how children who were hospitalized were treated versus children who were managed as an outpatient.[57] Only 44% received timely anatomic imaging, and 51% were on prophylaxis between the time of initial diagnosis of the UTI and subsequent imaging.

Urinary Tract Infection

The highest incidence of UTI is in the first year of life, with a strong male predominance.[58] Most infections during the first year of life are pyelonephritis, whereas most UTIs in older children are cystitis. The recurrence rate for UTI among girls is 30% within 1 year and 50% within 5 years. The recurrence rate in boys is 15%, with a significant drop-off after age 1 year.[58] The male predominance of febrile infections in infants younger than age 1 year corresponds to the incidence of reflux and bacteriuria in this age group. Among newborns, there is a bacteriuria rate of 1% to 1.5%, with a male predominance.[59-63] After the first year of life, bacteriuria becomes common in girls (3:1 to 4:1). This transition in sex distribution also is seen in the reflux incidence among toddlers and older children.[55,60]

UTI is a common bacterial disease of childhood. In a survey of Swedish 7-year-old schoolchildren, nearly 8% of the girls and 2% of the boys were found to have symptomatic UTIs confirmed by urine culture.[64] Among large studies of bacteriuria in older children, Kunin and associates[65] in 1962 found 1.1% to have asymptomatic bacteriuria. Renal scarring was found in 16%. The Newcastle Asymptomatic Bacteriuria Research Group obtained urine cultures in 15,000 schoolchildren 5 to 18 years old.[66] Only 0.2% of the boys had bacteriuria. Of the girls, overall 1.9% had asymptomatic bacteriuria, with the largest cohort being 7 to 10 years old. Renal scarring was found in 15%. The scarring rate increased to 19% for ages 4 to 6 years and 23% for ages 12 to 13 years. The rate decreased to 3.5% for age 15 years and older. Scarring was associated with higher grades of reflux (using the IRS system, grades III or higher). There was no association of symptoms with scarring. Although the peak incidence of bacteriuria occurred in children 7 to 10 years old, the peak incidence of scarring was seen in older children 12 to 13 years old.

A later study conducted by the Cardiff-Oxford Bacteriuria Study Group reported on the 4-year follow-up of 208 schoolgirls with bacteriuria 5 to 12 years old.[67] Reflux was found in 37%. Renal scarring was present in 22%. Kidneys that did not have scars at initial presentation did not develop new scars. Initial scarring progressed in 27%. Of these children 86% had reflux. Renal scar progression was not affected by antibiotic treatment. The low rate of progression of scarring in the patients who did not receive treatment led some investigators to conclude that in children with bacteriuria and an initially normal upper tract, follow-up was unnecessary. They argued that less than 2% of all the children with bacteriuria would benefit from further investigation and treatment. This situation led to the concept of a "top-down" evaluation. Rather than ordering a VCUG, the initial study in the evaluation of a child with a culture-proven UTI is a Tc^{99m}-DMSA scan. If there is no evidence of scarring or pyelonephritis, the VCUG is deferred.[68]

Renal Scarring

The frequency of renal scarring with pyelonephritis and reflux is proportional to the severity of reflux. Jodal[69] noted that children who presented with their first UTI with grades I and II had a scarring rate of 10% and 17%. This combined total of 27% is significantly lower than the 66% rate of scarring seen in grades III and higher. Renal scarring is directly related to the frequency of pyelonephritic episodes. Only 9% with one episode had scarring, whereas 35% of patients with three attacks had scarring, and 58% with four or more attacks had scarring. Infancy and prior pyelonephritis have been identified as strong positive predictors of risk for renal scarring. Pylkkanen and colleagues[70] found that infants younger than age 1 year had the highest risk of scarring and the highest incidence of congenital urinary tract anomalies.

The youngest children are at the greatest risk for renal scarring from bacterial pyelonephritis. Contributing factors are a low intrarenal reflux pressure, immature immune system, and delayed recognition of pyelonephritis or inadequate treatment.[71] It has been proposed that most of the renal scarring observed in older children occurs during the earliest childhood years as the result of a devastating injury (the "Big Bang").[58] If the youngest children are most vulnerable to scar formation, and adults rarely develop scars, would it be possible to define an age when the likelihood of scar formation becomes clinically insignificant?

Smellie and coworkers[72] in 1998 reported on the outcome of childhood reflux in 226 patients. Renal scarring was seen in 38%. No new scars developed after puberty. Naseer and Steinhardt[73] reported on 1062 patients with reflux followed for 9 years. Renal scarring was present in 13.5% at the time of diagnosis, and 2.1% developed new scars.[26] Only one patient who developed new scars had a normal kidney initially. Vernon and associates[74] reported on the development of new renal scars in 3- and 4-year-old children with reflux while on prophylaxis. The rates of breakthrough infection were similar between the two age groups: 27% for 3-year-olds, and 31% for 4-year-olds. New renal scars were found in 2.4% of 3-year-olds and in none of the 4-year-olds. The children who developed new scars were all younger than 3.4 years old at original presentation. The authors estimate that there was only a 2.5% risk of developing a new renal scar in children with a history of UTI and reflux, but a normal upper tract at presentation at age 3 years. This risk approached zero by age 4 years. Cooper and colleagues[75] examined the new renal scar rate in patients being followed for reflux. Over a 14-year period, 51 children with reflux were taken off of all prophylactic antibiotics. Reflux persisted in most, with only 19.6% resolving spontaneously off of antibiotics. Only 11.8% developed a subsequent UTI. No gross renal scars developed, but subtle new scars may be missed because only ultrasonography was used to assess the kidneys.

Many children scar because of UTI related to VUR and are at risk for future scars. There are nonetheless some children with VUR who are much less susceptible. Studies suggest that these particular patients may be at minimal risk of developing new scars even off of antibiotics. Al-Sayyad and coworkers[76] followed 78 patients off of antibiotics, and none developed new scars. Gordon and associates[77] in a meta-analysis found that VUR of infected urine is not always associated with renal scarring even in children hospitalized for pyelonephritis or febrile UTI. Garin and colleagues,[78] in a multicenter randomized controlled study, found that after 1 year, patients with VUR did not have an increased incidence of renal scarring, UTI, or episodes of pyelonephritis compared with patients with no VUR regardless of antibiotic prophylaxis. The study's conclusions were criticized, however, for being drawn from only 1 year of follow-up.

When to Test for Reflux

The relative infrequency of UTI in boys has led to the recommendation that all boys with an infection be evaluated.[21,23,79] Conversely, the higher frequency of bacteriuria in girls has caused some to recommend delaying imaging if girls have had only "one infection."[21,23,79] The recall of whether the first UTI is truly the first infection is very tenuous.[22] Febrile episodes are often mistakenly attributed to a "sore throat" or "otitis media." Finally, many large studies have shown a 30 to 50% incidence of reflux in boys and girls after their first infection.[56]

It has been postulated that bladder epithelial inflammation during acute cystitis might affect the function of the ureterovesical junction. Cystograms performed during ongoing urinary infections might falsely show reflux that is not present in sterile urine. This has not been shown to be valid. In a 12-month survey of 601 children (with urine cultures taken at the time of study) being evaluated by VCUG, Gross and Lebowitz[80] correlated the urine culture results and the presence of reflux. Reflux was found in 34%; 88% of these children had sterile urine, and 12% had infected urine. Of the 66% who did not have reflux, 90% had sterile urine, and 10% were infected. These data do not support the contention that reflux is secondary to UTI. It is reasonable to make a diagnosis on the results of a VCUG done in the presence of a positive urine culture. For patient comfort, one may delay scheduling the imaging study until symptoms have abated. A study in 1997 found that a VCUG can be performed 1 week after treatment without affecting the validity of the results.[79]

The question of whom to test for reflux is a complex one. The literature regarding bacteriuria and epidemiology of renal scarring is sometimes contradictory. Some authorities stress the rarity of new renal scarring in older children and do not recommend evaluation beyond a fixed age.[15,67] The justification is that if the principal danger of reflux is renal scarring, and if renal scarring is unlikely to occur beyond a certain age, it is unnecessary to image for reflux beyond a certain age as well. The importance of the initial presence of renal scarring as a predictor of future scarring and the sequelae of reflux nephropathy has been cited. Children with normal kidneys without scarring at initial presentation are also not thought by some to be at sufficient risk to warrant further imaging for reflux—hence, the previously discussed "top down" approach.[68] The previously discussed studies of bacteriuric children show, however, that the largest proportion of children with newly discovered renal scarring are older than 5 years.[66] Peak bacteriuria rates have been reported between age 7 and 10 years, and peak scarring rates have been reported between age 12 and 13 years. Each physician should keep these concerns in mind when deciding whom to image for reflux.

Familial Reflux

Identical twins have been observed to have reflux.[81,82] Reflux occurs in the siblings of affected children at a significantly higher rate than that in the general pediatric population.[83-87] Although the exact form of genetic transmission is not yet established, it has been determined that when one child has reflux, other siblings are at enough risk to warrant evaluation.

The sibling reflux rate has been estimated to be 40% to 50%.[85,88] Jerkins and Noe[84] studied 104 siblings, and 32% were found to have reflux. Most of these siblings with reflux (73%) had no history of UTI or abnormal voiding symptoms. Aggarwal and Verrier Jones[89] in 1989 reported on screening of first-degree relatives using ultrasound and IVP. Of 52 relations tested, 23% were found to have reflux. This study was restricted to only relatives who were younger than 2 years or older than 2 years and with an upper tract abnormality detected on ultrasound or IVP. Peeden and Noe[85] studied 24 siblings and found a 46% reflux rate. In a dual-center study of 422 families comprising 622 siblings, reflux was found in 27%.[83] Most (77%) had grade II or III. The rate was 20% in boys and 33% in girls. Reflux nephropathy was shown by renal scan in 13.6%. Evaluation of older siblings is controversial because they account for only a small fraction of all siblings with reflux, yet can have a significant proportion of renal scarring. Only 5% of the positive siblings were 10 years old or older, but in this group 27% had reflux nephropathy.

The natural history of reflux in siblings is similar to that of the probands.[90] Finally, the economic cost of screening has been investigated. If the rate of detection among siblings were only 1%, the early discovery and management would yield cost savings beyond the cost of screening all siblings. This includes the prevention of the potential consequences of reflux in these siblings: hypertension, renal scarring, renal insufficiency, dialysis, and transplantation.[91]

The recognition of hereditary VUR has led to efforts to identify and isolate the associated genes. Autosomal dominant inheritance is most likely, but because of variable penetrance and expressivity, large multigenerational pedigrees traceable to linkage analysis have yet to be assembled. Sanna-Cherchi and colleagues[92] noted that single genome-wide studies of familial VUR have shown a linkage to chromosomes 6p21, 1p13, 10q26, and 19q13.[93,94] Despite sufficient power, linkage of familial VUR to previously reported candidate intervals has not been reliably replicated. There is substantial heterogeneity, and any mapping strategy would need a large number of kindreds or proband loaded pedigrees.

Racial Differences

Children of Asian and African ancestry have a lower incidence of reflux.[95-97] In a study of the medical management of reflux, only 6% of the children were African American, and 2% were Asian.[95] In another study of antenatal hydronephrosis, 53% of whom were African American, the incidence of reflux was zero among the African Americans, and 17.6% in all the other children.[98] Askari and Belman[97] found reflux in only 10% of African American girls after a culture-proven infection. In a study of primary reflux in African American children, Skoog and Belman[99] found a 23% incidence of renal scarring. Although there are racial differences in the incidence of reflux,

Table 23-3 Conditions Associated with Primary Vesicoureteral Reflux

Renal agenesis
Horseshoe kidney and renal ectopia
Multicystic dysplastic kidney
Prune-belly syndrome
Megacystis-megaureter syndrome
Hypospadias
Duplication, ureterocele, ectopic ureter
Imperforate anus
Pretransplant evaluation
Complex syndromes with neurogenic and genitourinary manifestations

all patients at risk for reflux should be thoroughly evaluated regardless of race.

Antenatal Hydronephrosis

In a study of 130 neonates with antenatal hydronephrosis, 38% were found to have reflux, and 49% of these were bilateral.[100] Burge and associates[101] found 18% of infants with antenatal hydronephrosis to have reflux. Normal postpartum ultrasound scans are found in 60% to 80% of infants with antenatal hydronephrosis who have VUR.[102,103] It is necessary to perform a cystogram on all infants discovered to have antenatal hydronephrosis, despite a normal postpartum ultrasound scan. In contrast to older children, there is a different sex distribution. Instead of the usual female predominance (approximately 3:1), among antenatal hydronephrosis patients there is a higher percentage of boys. Anderson and Rickwood[104] found a 91% male predominance. Oliveira and coworkers[105] found that 86% were boys. Gordon and associates[106] found a similar rate (84%). The severity of reflux is greater, with grade III or higher being more prevalent. Elder[107] found that 80% of antenatally diagnosed reflux is at least grade III. These children may have other genitourinary anomalies, with ureteropelvic junction obstruction being the most common after reflux.[104,106]

Associated Conditions

Many conditions are associated with reflux (Table 23-3). The site of origin of the ureteral bud from the wolffian duct plays a crucial role in determining the subsequent development of the ureter and associated kidney. Abnormalities in adjacent organs, such as the bladder, urethra, rectum, or sacrum, should suggest the possibility of reflux.

RENAL ANOMALIES

Where there is only one functional kidney, the presence of contralateral reflux should be investigated. True renal agenesis, a rare occurrence, has a very high rate of contralateral reflux. More than one third of patients have contralateral reflux.[108] Similarly, multicystic dysplastic kidney has a high contralateral reflux rate. Flack and Bellinger[109] noted that in children with multicystic dysplastic kidney and contralateral reflux, 75% of the refluxing kidneys had a normal ultrasound scan. A cystogram should be performed in all of these patients. Children with horseshoe kidneys have a higher than normal incidence of reflux.[110] Guarino and colleagues[111] found that the natural history of VUR associated with renal anomalies (e.g., renal agenesis, multicystic dysplastic kidney, renal ectopia) is generally favorable, with comparable resolution rates.

HYPOSPADIAS

Hypospadias is associated with other congenital anomalies of the genitourinary tract.[112,113] Shafir and colleagues[113] found a reflux rate of 19%, and the presence of VUR in conjunction with complex genitourinary anomalies should not be surprising.[114] Routine evaluation of these boys is not widely recommended, however, because most of the reflux seems to be low grade and not associated with UTI or pyelonephritis. A cystogram should be performed if there are UTIs.

MEDICAL MANAGEMENT

Observation without Continuous Prophylaxis: Historical Data

During the 1960s and 1970s, early investigators observed large groups of children with reflux without continuous prophylaxis and treated each infection as it occurred. The International Scale had not been adopted at the time of all these investigations, so descriptive terms were often used to differentiate high-grade and low-grade VUR. The experience of Lenaghan and coworkers[115-117] helped establish the need for continuous prophylaxis. These investigators followed children for up to 18 years, and UTIs were treated intermittently as they appeared. In Lenaghan's series, the average age of boys at diagnosis was less than 1 year, and the average age of girls was 7 years. The overall cessation rate was 42%. Unilateral reflux without ureteral dilation seemed slightly more likely to resolve (65%) than bilateral reflux (50%), whereas bilateral reflux with dilation almost never resolved (26%).

Renal damage, as observed on IVP, occurred even after one infection. New renal damage was more likely in kidneys with previous scarring, but could occur in normal kidneys. Of the group with normal kidneys, 21% developed new scars; of the group with preexisting scars, 66% developed new scars. Most proven infections occurred within the first 5 years of diagnosis. Of this population, 36% had scars at diagnosis, and 10% developed hypertension. Most new scars were seen in girls.[116] No boys had infections after reflux stopped, and 40% of girls continued to have episodes of infection after reflux stopped. Lenaghan[116] concluded that intermittent treatment of infection led to an unacceptably high rate of new scar formation in all children.

Data from the International Reflux Study in Children (IRSC) showed a high rate of new scar formation in children observed off of continuous prophylaxis.[118] In this series, new scars occurred in 12.5% of children with normal kidneys, whereas 62% of scarred kidneys showed progression if the infections were treated only intermittently. Many of the children with new scars were older than 7 years. Govan and associates[119] observed girls with reflux while not on continuous prophylaxis. During the observation period, 50% of these children had UTIs, and 20% of this group had pyelonephritis. Scarring did not occur in all renal units despite having had infections. More scarring occurred in reflux with ureteral dilation, although 23% of girls with grade I reflux developed new scars. O'Donnell and colleagues[120] observed a cohort of children without continuous prophylaxis, and infections were treated after they were diagnosed; 35% developed new scars. A group followed at the same time while on continuous prophylaxis had only a 9% rate of new scar formation.

The conclusion that emerged from these earliest studies was that treating each infection after it was diagnosed was unsafe. Not all children developed scars, but it was impossible to predict who those children might be. Although girls seemed more vulnerable to infection and new scar formation, not all boys could avoid those consequences. Children of all ages could develop scars, as could children with the least amounts of reflux. Preexisting renal scarring seemed to suggest that the individual was at risk for scar progression with additional infections, but new scars were also seen in previously unscarred kidneys.

Studies with Continuous Prophylaxis

Continuous Prophylaxis Studies: All Grades

In Goldraich and Goldraich's large prospective study,[121] following children on long-term prophylaxis with all grades of reflux, there was a 3% rate of new scar formation in girls and boys, and these were seen only in association with breakthrough infection. None of the children who developed new scars were older than 4 years. These authors did not consider asymptomatic breakthrough infection significant. They concluded that it was unnecessary to keep children on prophylaxis beyond age 5 years. Two consecutive cystograms were necessary before stopping prophylaxis. Bilateral high-grade reflux seemed to resolve less often than unilateral reflux.

Arant[95] followed 59 patients with low-grade (I to III) reflux for 5 years. All children were younger than 5 years old when they entered the study. Thirty-four percent had a breakthrough infection. Resolution rates were grade I, 82%; grade II, 80%; and grade III, 46%. Unilateral reflux resolved slightly more often than bilateral reflux. No age-related difference in resolution was observed. Five new scars were seen after breakthrough infection. Compliance with a medical regimen varied, ranging from 75% in Dallas, Texas, to 12% in Little Rock, Arkansas. Arant[95] concluded that even low-grade reflux can be associated with renal damage.

Skoog and coworkers[122] observed 545 children on continuous low-dose antibiotic prophylaxis for 6 months to 10 years. A single-isotope VCUG was used to judge cessation. The follow-up rate was 88%. Thirteen percent ultimately underwent reimplantation surgery. The indications for surgery were breakthrough infection, high reflux grade, high reflux grade in adolescence, new renal scars, progressive renal insufficiency, poor compliance, or UTI after antibiotics were stopped. Resolution rates were grade I, 83%; grade II, 60%; grade III, 46%; grade IV, 9%; and grade V, 0%. The mean age of resolution was 4.6 years, and the mean time to resolution was 1.7 years. If the child was diagnosed before 1 year of age, the mean time to resolution was 1.4 years. Only 3 of 545 patients had progressive scars (0.5%), and 2 of these 3 had breakthrough infections. No decrease in renal function was seen using radionuclide scanning.

Birmingham (United Kingdom) Cooperative Study

The results of the Birmingham (United Kingdom) cooperative study were published at the 2-year and 5-year follow-up periods.[123,124] Children with severe dilating reflux or nondilating reflux with scars were prospectively followed. The International Scale was not used. The children were divided into a medical (continuous prophylaxis) and a surgical group and followed for 5 years. They were placed on trimethoprim, trimethoprim-sulfamethoxazole, or nitrofurantoin. Urine cultures were obtained every 3 months for 2 years and then every 6 months. Renal function was studied at 2 and 5 years with creatinine clearance and water deprivation tests. The investigators found no difference between the groups in rates of breakthrough UTI, renal function, renal growth, or progression of old scars or development of new scars. The rate of breakthrough infection was 25% in both groups, but these authors did not distinguish between cystitis and pyelonephritis. Of children with dilating reflux, 50% were still refluxing at 5 years. Some decrease was seen in the renal concentrating ability in older children who were medically managed. There was no difference in somatic growth between the surgical and the nonsurgical groups. The authors concluded that surgery and long-term prophylaxis were equally effective in preventing renal scarring.

International Reflux Study in Children: Grades III and IV

The IRSC, which was organized by centers in Europe and the United States, addressed grades III and IV reflux in children younger than 10 years old. The study compared medical (continuous prophylaxis) and surgical management.[3,118,125-130] The patients were followed for 5 years. All of these children presented with UTI, and 50% had renal scarring at entry. When stratified by age (<2 to >5 years old), the incidence of scarring at entry was comparable for each age group (50%). There was a high spontaneous resolution rate in medically managed patients—80% in undilated ureters (grade III). If there was ureteral dilation (grade IV), however, resolution was less likely. Of patients with grade IV reflux, 75% were still refluxing at the end of the study. The presence or absence of scarring did not correlate with cessation of reflux. There was no difference in the cessation rate between girls and boys.

Overall, unilateral reflux resolved more often (54%) than bilateral reflux (12%). Resolution was defined as two negative cystograms performed 2 years apart. Of children on continuous prophylaxis, 16% developed new scars or parenchymal thinning, and these children had breakthrough infection while on prophylaxis. Most scars developed in children younger than 5 years, although some were older. New scars were slightly more common in boys (18%) than in girls (11%).

A similar number of children who had surgery also developed new scars or parenchymal thinning (17%); however, almost all had postoperative obstruction or had scars seen 6 months after surgery, suggesting that the scarring was due to episodes of preoperative pyelonephritis or postoperative surgical complications. There was a clear difference in the rate of pyelonephritis, with many fewer episodes in the surgical group. The rates of cystitis were the same.

Compliance with the long-term medical regimen was 90%. During the observation period, there were no new cases of hypertension, and glomerular filtration rate was not reduced in any patient. Renal growth was the same between the medical and the surgical groups. Medical management was abandoned in 14 patients (20%) who developed two breakthrough infections. The overall breakthrough infection rate was 37%. One third (33%) had additional episodes of cystitis after reflux stopped. Age at entry did not affect the cessation rate. Worsening of reflux was rare.

The European arm of the IRSC published the results of Tc^{99m}-DMSA scanning in 287 children with grades III and IV reflux who were managed medically or surgically and followed for 5 years.[131] These patients were unusual in that 82% had scars at entry into the study. The number of new scars seen or deterioration in renal function was equal in surgical and medical groups. There were more febrile UTIs in the medically managed patients. Most of the new scars in the surgical group were noted within 1 year of surgery, implying that these scars occurred secondary to infections sustained before surgery or postoperative surgical complications. In addition, more new scars were seen in grade IV patients while on antibiotic prophylaxis.

Contemporary Data

Smellie and associates[132] more recently published a series of 52 children (25 girls, 27 boys), 1 to 12 years old, with grades III and IV bilateral reflux and bilateral renal scarring. They were randomly assigned to surgical or medical (prophylaxis) management and followed for 4 years. No new scars were seen in either group, and glomerular filtration rate remained unchanged. Recurrent UTIs occurred in 11 (40%) of the medically managed and 6 (24%) of the surgically managed children. Smellie and associates[132] concluded that surgery and medical therapy were equal in protecting renal integrity and function in this group of children with relatively severe reflux nephropathy.

Wheeler and colleagues[133] more recently published a meta-analysis of seven randomized, controlled clinical trials comparing continuous prophylaxis with surgery. This meta-analysis included the trials detailed previously. The overall risk of febrile and nonfebrile UTI occurring in either group was the same after 5 years. Similarly, the risk of new renal scarring was the same in both groups at 5 years of follow-up. End-stage renal failure and hypertension were poorly reported, and numbers were too small for analysis. They concluded that if there was a benefit to surgery over prophylaxis, it was minimal.

Prophylaxis and Surveillance Regimens

The most commonly recommended antibiotics in most published clinical studies are trimethoprim-sulfamethoxazole, nitrofurantoin, and nalidixic acid.[119,134-139] The reasons for drug choice include good urinary levels, effectiveness against urinary pathogens, minimal effect on bowel flora, palatability, and minimal side effects.[138] Cefaclor is commonly used in Japan because nitrofurantoin is unavailable.[140] The frequency of follow-up urinary cultures has varied from four times to twice a year.[139,141] Bloom and Bennet[142] suggested obtaining cultures only once a year for children older than 6 years because new renal scarring is less common in older children (see later discussion).

A modified form of continuous prophylaxis with trimethoprim-sulfamethoxazole every other day has been reported.[143] None of the boys in this small series developed infection, but 20% of the girls did. Continuous daily prophylaxis seems necessary while observing children with reflux.

The experience derived from these clinical studies suggests that VCUGs should be performed no more frequently than once a year. Some clinicians advocate repeating these studies every 18 months.[142,144] The reason is that reflux resolves slowly; approximately 20% to 30% resolve every 2 years.[139] More recently, computerized modeling has been used in an attempt to reduce the frequency of VCUGs.[9,145] Imaging performed every 2 or 3 years may be reasonable in certain instances. Given the lower resolution rate of grades IV and V reflux, VCUGs every 3 years would result in lower radiation exposure, discomfort, and cost.[9] This has to be counterbalanced against keeping a child on antibiotics for longer than may be necessary because the reflux may have resolved years before a negative VCUG is obtained. Two consecutive VCUGs, 1 year apart, have been recommended to be certain that the reflux has really resolved.[139] Approximately 30% of children with one negative VCUG have a positive test 1 year later.[139,144]

Patient Compliance

When continuous antibiotic prophylaxis was first proposed, it was assumed that good compliance would be necessary over many years.[135] Lack of compliance is a reason to abandon this regimen and suggest surgery. Most noncompliant families never return, however, either for prophylaxis management or to discuss surgery.[144] Compliance rates ranging from 12% to 90% have been reported. Skoog and coworkers[122] reported a compliance rate of 88%. The IRS reported compliance rates of 90%, but this was a prospective investigation in patients with high-grade reflux and renal scars.[3] Families entered the study after signing consent forms and knowing that they were to be followed for many years. Parents are more likely to be concerned under those circumstances. Arant[95] reported compliance rates of only 12% in families whose children had low-grade reflux.

The compliance issues in a large cohort of children who presented with low-grade reflux (grades I to III) were examined.[56,146] One third of patients failed to comply with a long-term regimen. Most of these noncompliant families (80%) failed to return after the first year. An analysis of socioeconomic factors revealed that there were no predictable underlying factors except maternal age. Mothers older than 36 years were more likely to continue bringing their children back. There was remarkable similarity between compliant and noncompliant groups. There were no significant age or sex differences. Factors such as income, level of parental education, type of medical insurance, type of primary care physician, and distance from hospital-based specialists all had no bearing (Figs. 23-6 and 23-7). Affluent and indigent families had similar rates of noncompliance. Prescription programs, which paid for medication, did not increase compliance. In a cohort of more than 35,000 patients with VUR followed for 2 years, all of whom had insurance-provided pharmacy services, Hensle and coworkers[147] reported that only 17% of patients placed on long-term prophylaxis remained adherent.

Regardless of the circumstances, a certain number of families are not going to maintain a regimen of prophylaxis, surveillance urine cultures, and repetitive radiographic examinations over many years. This situation challenges the clinician to devise strategies to increase compliance or

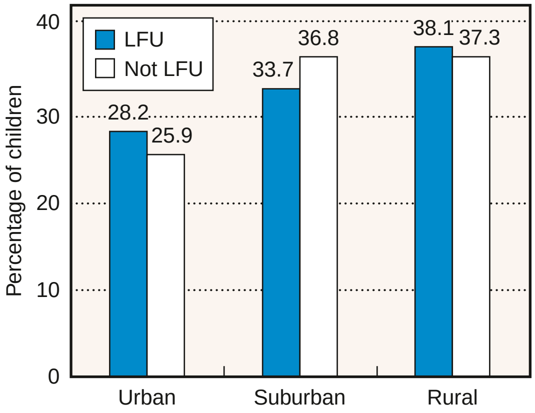

Figure 23-6 Percentage of children on antibiotic prophylaxis, grouped by locality and distance from urban pediatric specialty care center, who became lost to follow-up (LFU) and who remained under observation (Not LFU). (Redrawn from Greenfield SP, Wan J. Vesicoureteral reflux: practical aspects of evaluation and management. *Pediatr Nephrol.* 1996;10:789. Copyright © 1996 by Springer-Verlag.)

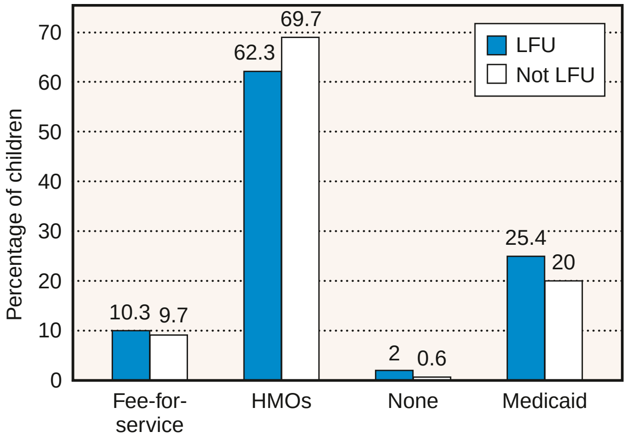

Figure 23-7 Percentage of children on antibiotic prophylaxis, grouped by medical insurance, who became lost to follow-up (LFU) and who remained under observation (Not LFU). Medicaid, state-funded insurance for indigent families; HMO, Health Maintenance Organization, a managed-care insurance scheme with rigid control of specialist referrals and assignment to primary care physicians; fee-for-service, traditional insurance with no restriction on specialist referrals or primary care physician assignment. (Redrawn from Greenfield SP, Wan J. Vesicoureteral reflux: practical aspects of evaluation and management. *Pediatr Nephrol.* 1996;10:789. Copyright © 1996 by Springer-Verlag.)

to identify patients who might benefit from early surgery or endoscopic therapy. Ogan and colleagues[148] reported that most families opted for long-term prophylaxis if they believed that the reflux would resolve within 4 years. In addition, if low-grade reflux persisted for more than 3 years, most families opted to switch to endoscopic correction, rather than continue surveillance.

Breakthrough Infection

Breakthrough infection is defined as the development of an infection with an organism resistant to prophylaxis.[144] Breakthrough infections are more frequent in girls, but they can occur in boys.[144,135,149] Breakthrough infection rates vary, depending on the range of children followed. The IRSC followed children with only grades III and IV reflux, and many had preexisting scars. The IRSC reported a breakthrough infection rate of 37%.[128] If children with all grades are followed, breakthrough infection rates vary from 10% to 25%.[144,124,150] In one series of 62 children with documented breakthrough infection, 60 were girls and 2 were boys (Table 23-4).[144] The grades of reflux present in these 62 patients were grade I in 2, grade II in 19, grade III in 24, grade IV in 14, and grade V in 3; 70% had low-grade reflux. The age distribution was as follows: younger than 1 year, 3; 1 to 3 years, 14; 4 to 6 years, 24; 7 to 9 years, 15; and older than 10 years, 6. Although most children were younger, one third were at least 7 years old.

Breakthrough infections may be more common if there is voiding dysfunction (see later discussion).[151] If the organism is sensitive to the prophylactic antibiotic, one has to question the compliance of the family with taking daily medication, or perhaps the quality of the manufactured antibiotic.[149] These infections may be febrile, with lower tract symptoms only, or entirely asymptomatic. Scarring has been described after asymptomatic breakthrough infections, but many authorities state that only febrile infections are "significant."[121,135] Smellie and colleagues[135] found that two thirds of breakthrough infections associated with new scars were asymptomatic.

Table 23-4 Characteristics of 62 Children with Breakthrough Urinary Tract Infections

Grade*	No. Patients	Patient Age (yr)	No. Patients
I	2	<1	3
II	19	1-3	14
III	24	4-6	24
IV	14	7-9	15
V	3	>10	6

*Higher grades noted when reflux was bilateral.
From Greenfield SP, Ng M, Wan J. Experience with vesicoureteral reflux in children: clinical characteristics. *J Urol.* 1997;158:574-577.

The number of breakthrough infections that can be safely tolerated before recommending surgery is not agreed on. Some authors suggest waiting for two breakthroughs, whereas others tolerate only one.[152,153] The IRSC considered medical management to fail if there were two episodes of febrile pyelonephritis or lower tract bacteriuria while the patient was receiving prophylaxis.[118]

There is a high incidence of recurrent UTI in girls after successful surgery or after spontaneous resolution. Scott[154] reported a 29% rate of cystitis after spontaneous resolution. Lenaghan[116] reported that no boys and 40% of girls had recurrent episodes of cystitis after cessation. A cystitis rate of 30% has been reported after reimplantation, and most of these children were girls who had undergone surgery because of breakthrough infection.[144] These data suggest that certain girls are prone to infection without reflux being present, so the reflux alone is not responsible for their propensity to recurrent cystitis.

New Renal Scarring and Prophylaxis Regimens

New scarring almost exclusively occurs in association with infection. As noted previously, these infections and new scarring are more numerous without continuous prophylaxis. New scars can occur in children on prophylaxis if there is breakthrough infection. Smellie and associates[138,155] noted that most children with new renal scarring had experienced delays in diagnosis after a UTI, delays in treatment of episodes of pyelonephritis, and delays of physician-recommended screening for asymptomatic siblings.

New scarring can occur at any age, including adolescence, and with any grade.[136] Children with voiding dysfunction seem to get more breakthrough infections, and this may play a role in new renal scar formation (see later discussion).[156] Most scarring does occur earlier in life.[138] Winberg[157] noted that age 5 years is not sacrosanct, although children 5 years old and younger seem more vulnerable. Ditchfield and coworkers[158] found that most new scars developed in children younger than age 2 years, although they studied only children younger than age 5. The Birmingham study[123] found that most new scars occurred between ages 2 and 7 years, but established scars could progress at any age. Kidneys with previous scars also are more likely to get new scars, but new scars also occur in previously normal kidneys, although at a lower rate.[118,157]

Age as a Predictor

Shimada and colleagues[159] found that new renal scars resulting from breakthrough infection could occur in older children while being observed on prophylaxis for reflux. In a group of 923 children followed on prophylaxis, the mean age of individuals with new scars was 7 years, 10 months, and one quarter of children with new scars were older than 10 years when a new scar was seen. Smellie and Edwards and their colleagues[135,139] observed fresh scars in previously normal kidneys in children, including boys, 10 years old. In an early study by Smellie and coworkers[160] of children with scars, new scars most often occurred in children older than 5 years; most scars were in girls, although 20% were in boys; the infection associated with the new scar could be febrile, afebrile with lower urinary symptoms, or totally asymptomatic; and the infection could be seen in all grades, although most were in high-grade reflux with dilated ureters. Many of these children and families were poorly compliant with continuous prophylactic regimens. Naseer and Steinhardt[156] found that of 31 children identified with new scars, 12 (39%) were 8 years or older, and 4 (13%) were teenagers.

Radiographic Predictors

Apart from grade, other aspects of radiographic imaging may help predict who is most susceptible to renal scarring. Using radionuclide cystography, McLaren and Simpson[161] correlated high renal scar rates with reflux occurring at low bladder volumes. Mingin and colleagues[162] showed that breakthrough infection is more common in children who have an initial scan with scarring. They retrospectively reviewed the records of 120 infants who were first identified with VUR owing to prenatal hydronephrosis and who were followed for 4 years. Of the group with an initial scar seen on Tc^{99m}-DMSA scan, 60% developed a breakthrough infection, whereas only 8% of the group without an initial scar developed a breakthrough infection. In a study of 38 patients with breakthrough infections by Szlyk and coworkers,[163] however, 10% were found to have a new scar, and 75% of those had a normal baseline renal scan. Radionuclide scanning may be able to identify patients at highest risk, but a normal renal scan does not guarantee that a breakthrough infection and new renal scar would not occur.

Micromolecular and Genetic Predictors of Scarring

Some children may have a genetic predisposition to renal scarring, on or off prophylaxis. It has been shown that individuals with DD genotype of the angiotensin-converting enzyme gene were at increased risk of scarring.[164] Conversely, in a group of siblings with VUR, Yoneda and associates[165] did not find an association between the DD genotype and scarring. Patients with reflux and tumor necrosis factor-α AA genotypes have increased rates of renal scarring compared with nonrefluxing controls.[166] Tumor necrosis factor-α is a proinflammatory cytokine that stimulates growth factors that result in matrix deposition and fibrosis. The genetic alleles of tissue kallikrein promoter and transforming growth factor-β1 were found to be similar in Taiwanese children with more severe renal scarring.[167] Insulin-like growth factor-I mRNA expression has been found to be significantly reduced in the proximal tubules in tissue specimens from scarred kidneys compared with controls.[168] Downregulation of the genes responsible also may result in increased interstitial collagen deposition.

Cytokines such as interleukin-6 and interleukin-8 are produced by epithelial cells in response to inflammatory damage.[45,169] Interleukin-8 has been shown to be elevated in patients with VUR and no ongoing infection.[45] Increases of urinary interleukin-6 have been found in patients with severe scarring.[169] Cyclooxygenase-2 overexpression in proximal tubules and the tubulointerstitial space has been found in renal tissue from kidneys with severe renal scars.[170] It is theorized that this overexpression is related to increased renin and angiotensin II production, leading to interstitial fibrosis. Urinary endothelin-1, a vasoconstrictor peptide produced by mesangial and tubular epithelial cells, also has been found to be increased in the tissues of kidneys with severe renal scarring and interstitial fibrosis.[171] Urinary endothelin-1 may be a marker for scarring or for kidneys susceptible to scarring.

Discontinuing Prophylaxis

Some authors have recommended stopping prophylaxis after a certain age in boys and girls. The rationale is that most, but not all, new scarring occurs in younger children, as outlined previously. Belman and Skoog[134] suggested stopping prophylaxis after age 7 years, and Winberg[157] suggested age 5 years. Cooper and colleagues[75] reported on a series of 51 children (40 girls, 11 boys) in whom prophylaxis was stopped. Their ages ranged from 3 to 14 years, and not all children had contrast cystograms, so the grade was not always known when prophylaxis was stopped. Six children (five girls, one boy) returned with UTIs. No new scars were seen after infection, but only renal ultrasound scans were performed, so new renal scars might not have been seen.

Similarly, Thompson and colleagues[172] discontinued prophylaxis in a large group of children with known reflux at a mean age of 6 years, and one third developed urinary infections. New scars were seen on renal scanning in seven children off prophylaxis, all of whom had grade II or III reflux. Many children in this study did not have renal radionuclide scans, so many new scars could have been overlooked. Georgaki-Angelaki and coworkers[173] reported on a cohort of 54 children who had antibiotics stopped and were then followed for 4 years. None had had a breakthrough infection for 2 years before stopping antibiotics. None had hydronephrosis, voiding dysfunction, or a new renal scar found on previous renal scanning. The average age was 6 years at the time of stopping antibiotics. Greater than 90% had grade III reflux or less. Routine urine cultures were obtained *monthly* and after any fever or lower urinary tract symptoms. There were only eight infection episodes, and no new renal scars were seen on Tc^{99m}-DMSA scanning. In this aggressively observed population of older children with low-grade reflux, stopping prophylaxis was safe.

There are no large, long-term, prospective studies that establish safe guidelines for discontinuing prophylaxis based on grade, sex, race, renal scarring, or voiding habits. Until these subpopulations are better defined, there is a risk to new renal scar formation if antibiotics are stopped before spontaneous cessation or surgical correction of VUR in boys or girls of any age through adolescence and with any grade of reflux, with or without preexisting scarring. In a survey of pediatric urologists, however, most stated that they would stop prophylaxis in patients with unresolved high-grade reflux at puberty.[174]

Spontaneous Resolution Rates

Cystoscopic Evaluation

Attempts have been made to correlate the cystoscopic findings of ureteral configuration and location with spontaneous cessation.[175] Although there seems to be a correlation with the grossest reflux and the most abnormal orifices, this is not true for most of the intermediate-grade and low-grade refluxing ureters.[176] Significant interobserver discrepancies exist when more than one physician looks at the same patient.[176]

Table 23-5 Percentage of Children Who Resolved Their Reflux While on Antibiotic Prophylaxis*

	GRADE				
Study	***I***	***II***	***III***	***IV***	***V***
Skoog et al[122] (1987)	83	60	46	9	0
Huang and Tsai[150] (1995)	92	76	62	32	0
Bellinger and Duckett[176] (1984)	87	63	53	33	
Greenfield et al[144] (1997)	69	56	49		
Arant[95] (1992)	82	80	46		

*Grouped by grade (international scale) as published in several studies

Cystoscopy does not often play a role in assessing children for the likelihood of spontaneous resolution.[177]

Early Observations

Early studies by Edwards and coworkers,[139] before the development of a widely accepted grading system, revealed that spontaneous cessation does occur in 85% of children whose ureters are not dilated, and in 40% of children whose ureters are dilated. These investigators also showed that reflux can stop at all ages, including midadolescence, and there was no way to predict when reflux would cease. Twenty percent to 30% of reflux disappeared every 2 years. Mulcahy and Kelalis[178] and Hutch[179] showed that cessation can occur after age 10 years, even as late as early adolescence. Lenaghan[116,117] observed spontaneous cessation in 15-year-olds.

Resolution and Grade

Belman and Skoog[134] reported on 545 children managed nonoperatively with all grades of reflux. The mean age at diagnosis was 3 years. The children were followed on continuous antibiotic prophylaxis with periodic VCUGs. Resolution rates were grade I, 83%; grade II, 60%; grade III, 46%; grade IV, 9%; and grade V, 0%. Thirty percent to 35% of the group that resolved did so each year. The mean age of resolution was 4.6 years, and the mean time to resolution among patients who resolved was 1.7 years. If the child was diagnosed younger than 1 year of age, the mean time to resolution was 1.4 years. Huang and Tsai[150] reported long-term resolution rates of grade I, 92%; grade II, 76%; grade III, 62%; grade IV, 32%; and grade V, 0%. Bellinger and Duckett[176] reported cessation rates of grade I, 87%; grade II, 63%; grade III, 53%; and grade IV, 33%. The average age of cessation was 6 years, and the mean time to cessation was 3 years. We reported similar resolution rates of low-grade reflux: grade I, 69%; grade II, 56%; and grade III, 49% (Table 23-5).[144] Schwab and associates[180] observed a resolution rate of 13% yearly if the grade was III or less, whereas 5% of grade IV and V patients resolved annually. In their study, boys resolved more rapidly than girls, and bilateral reflux seemed to resolve more slowly over time.

It is still impossible to predict definitively in whom reflux will resolve. The literature provides percentages of resolution based on grade, but this does not help the individual. Many studies use only one negative VCUG as an end point. This approach may overstate the resolution rate because 30% of children with one negative VCUG have a positive one later.[144,139] Data have been conflicting regarding the differences between the resolution rates of bilateral versus unilateral reflux. Most studies seem to show, however, that bilateral high-grade reflux with ureteral dilation apparently resolves less often than unilateral high-grade reflux.[181] The difference in resolution rates between bilateral and unilateral low-grade reflux is less marked (Table 23-6).

Kaplan-Meier curves have been used in an attempt to predict a time course for families. Using this type of analysis, Wennerstrom and associates[181] showed that 50% of children with grade I reflux should expect resolution within 2.5 years of diagnosis; with grade II reflux, within 5 years of diagnosis; and with grades III and IV, within 8 years of diagnosis. They also found that girls persisted a bit longer than boys grade for grade. Using Kaplan-Meier estimates, Esbjorner and colleagues[182] also found that boys more often and more rapidly resolved their reflux over time, even if it was dilating (high grade).

When looking at low-grade reflux alone (grades I to III), age at presentation and, by inference, age of the child do not predict the likelihood of resolution. An analysis of a large number of these patients found that there was no statistical difference when comparing resolution rates of children of different ages in these low grades (Fig. 23-8). Certain trends could be discerned, however. Resolution rates remained high (>40%) regardless of age. Resolution rates for older children (children 7 to 9 years old with grade II reflux, 70% resolution rate) could be higher than the resolution rates for infants (infants <1 year old with grade II reflux, 54% resolution rate). There also was no significant difference when comparing unilateral and bilateral reflux, or when comparing boys with girls grade for grade in these low grades. The standard deviations for the mean times to resolution were so great that these times were not useful when counseling individual families (Table 23-7).

Similarly, Connolly and associates[184] found that reflux resolution rates in girls older than 5 years were comparable to rates seen in infants. In their cohort, the percent of annual resolution was 20% each year until age 11 years. Most of their patients had “mild” or “moderate” reflux as graded on a nuclear cystogram. These data suggest that families and clinicians must expect VUR to persist for many years, possibly until adolescence. Older children have an equally good chance of resolving their low-grade reflux up to adolescence. Neither sex nor laterality can help predict resolution. Grade remains the best predictive parameter. Finally, although some studies consider grade I reflux “resolved,” this may not be accurate or clinically justified. Grmek and Fettich[185] found that 20% of children with initial grade I reflux had grade II (17%) or grade III (3%) seen on a second VCUG.

McLorie and colleagues[186] presented data regarding resolution rates of grades III and IV reflux, although patients were not stratified for age at the beginning of the observation period. After 2 years of observation, 80% of children with grades III and IV reflux were still refluxing, and 50% or more were still refluxing after 5 years. Neither sex nor laterality had a bearing on resolution rate. These investigators concluded that it was reasonable to recommend surgery if the reflux had not ceased after 4 years of observation, no matter what the age.

Siblings and Resolution

Reflux in siblings has the same rate of resolution as in the probands.[152] The grade is the determining factor. In a study of 108 asymptomatic siblings, resolution occurred in 53%, with a mean follow-up of 18 months, or 28% per year.[90] Only two

Table 23-6 Medical Therapy: Percent Chance of Reflux Resolution after Specified Number of Years*

Risk Category, Age (No. Patients on which Estimates Are Based)	PERCENT CHANCE (95% CONFIDENCE INTERVAL)				
	1 Year	*2 Year*	*3 Year*	*4 Year*	*5 Year*
Grade I†	39.3 (24.6-51.1)	63.1 (43.2-76.1)	77.6 (57.2-88.3)	86.4 (67.7-94.3)	91.8 (75.7-97.2)
Grade II† (*n* = 250)	28 (24.1-31.7)	48.1 (42.3-53.4)	62.7 (56.2-68.1)	73.1 (66.8-78.2)	80.6 (74.8-85.1)
Grade III, unilateral, age 0-24 mo (*n* = 27)	21.4 (10.8-30.8)	38.2 (20.4-52.1)	51.5 (29.0-66.8)	61.9 (36.6-77.1)	70 (43.5-84.1)
Grade III, unilateral, age 25-60 mo (*n* = 27)	13.4 (4.6-21.4)	25 (8.9-38.3)	35.1 (13.1-51.5)	43.8 (17.1-61.9)	51.3 (20.9-70.1)
Grade III, unilateral, age 61-120 mo (*n* = 15)	10.8 (3.5-17.5)	20.5 (6.9-32)	29.1 (10.2-43.9)	36.7 (13.4-53.8)	43.6 (16.5-61.9)
Grade III, bilateral, age 0-24 mo (*n* = 62)	12.7 (7.0-18.1)	23.8 (13.5-32.9)	33.5 (19.5-45.0)	41.9 (25.1-55.0)	49.3 (30.3-63.1)
Grade III, bilateral, age 25-60 mo (*n* = 53)	7 (3.1-10.8)	13.5 (6.1-20.4)	19.6 (9.0-28.9)	25.2 (11.8-36.6)	30.5 (14.6-43.4)
Grade III, bilateral, age 61-120 mo (*n* = 12)	2.6 (0.7-4.5)	5.2 (1.4-8.8)	7.7 (2.1-13.0)	10.1 (2.8-16.9)	12.5 (3.5-20.7)
Grade IV, unilateral‡ (*n* = 28)	16.1 (8.5-23.1)	29.7 (16.4-40.8)	41 (23.5-54.5)	50.5 (30.0-65.0)	58.5 (36.0-73.1)
Grade IV, bilateral‡ (*n* = 96)	4.5 (1.0-7.9)	6.4 (2.0-15.1)	7.8 (3.0-21.8)	8.9 (4.0-28.0)	9.9 (4.9-33.7)

*The yearly rate of reflux resolution remains constant for each group.
†No difference shown by age or laterality (unilateral/bilateral); these categories were combined.
‡Estimates apply only to the time of diagnosis and are not age specific.
From American Urologic Association. *Report on the Management of Primary Vesicoureteral Reflux in Children.* Baltimore: American Urologic Association; 1997.

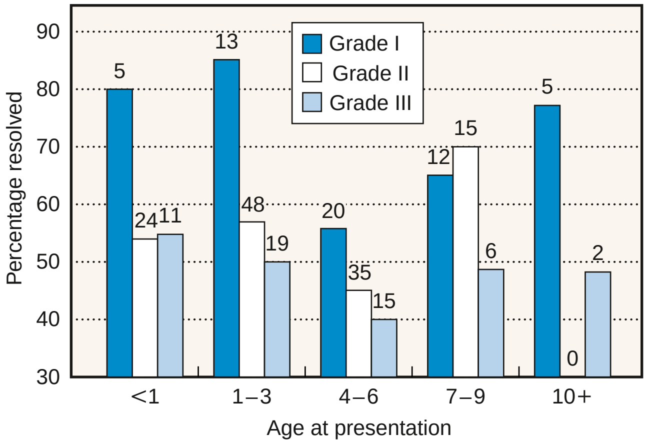

Figure 23-8 Resolution rates of vesicoureteral reflux, stratified by grade (I, II, and III) and age at presentation. (Redrawn from Greenfield SP, Ng M, Wan J. Resolution rates of low-grade vesicoureteral reflux stratified by patient age at presentation. *J Urol.* 1997;157:1410.)

children (2%) had a breakthrough infection while on prophylaxis, and eight children (7%) underwent surgery. These infection rates are lower than the rates reported for probands with reflux who present with UTIs. Parekh and associates[187] found that reflux in siblings seemed to resolve more quickly than in probands diagnosed after a UTI. In a group of 40 siblings, 84% resolved with observation, with a mean time to resolution of 16 months. All had grade III or less at presentation except one child with grade IV reflux.

Table 23-7 Months (Mean ± SD) to Resolution According to Highest Reflux Grade and Patient Age at Presentation

	REFLUX GRADE		
Age (yr)	*I*	*II*	*III*
<1	37.68 ± 24.5	14.51 ± 9.37	32.88 ± 32.3
1-3	17.69 ± 10.4	26.93 ± 17.57	22.56 ± 13.1
4-6	16.69 ± 8.85	22.51 ± 24.7	22.56 ± 26.8
7-9	26.52 ± 17.68	20.68 ± 11.9	22.56 ± 14.2
>10	14.69 ± 1.96		11.18

From Greenfield SP, Ng M, Wan J. Resolution rates of low grade vesicoureteral reflux stratified by patient age at presentation. *J Urol.* 1997;157:1410-1413.

Spontaneous Resolution and Special Anatomic Situations

Complete Ureteral Duplication

If there is complete ureteral duplication, reflux may occur in both ureters or only the lower pole. The Weigert-Meyer rule explains the phenomenon of lower pole reflux in this setting because the lower pole ureter always enters the bladder more lateral and cephalad than the upper pole ureter.[188] The lower pole ureter may have less of a subepithelial tunnel, whereas the tunnel of the upper pole ureter remains adequate to prevent reflux. Rarely, there can be upper pole reflux alone. In this circumstance, the Weigert-Meyer rule is still operative, but both ureteral orifices are shifted further caudad, so that now the lower pole ureter occupies a normal position on the trigone, whereas an upper pole ureter is ectopic to the bladder neck or below (Figs. 23-9 and 23-10).

Spontaneous resolution of reflux can occur in the setting of complete duplication, with certain qualifications.[189-191] High-grade lower pole reflux with ureteral dilation and lower pole atrophy has a low resolution rate, and some authors[189,192] advocate early surgical correction in that group. Fehrenbaker and colleagues[192] had no resolution of reflux in duplicated systems over a 5-year observation period, but all of their patients had high-grade lower pole reflux with cortical atrophy. Heminephrectomy may be indicated if there is no lower pole function. Ben-Ami and coworkers[189] noted that children with grade I or II reflux into the lower pole had a 44% resolution rate, with cessation seen at an average age of 2 years. They did not see anyone with grade III reflux resolve, and it is their policy to perform surgical correction patients with grade IV or greater reflux into the lower pole.

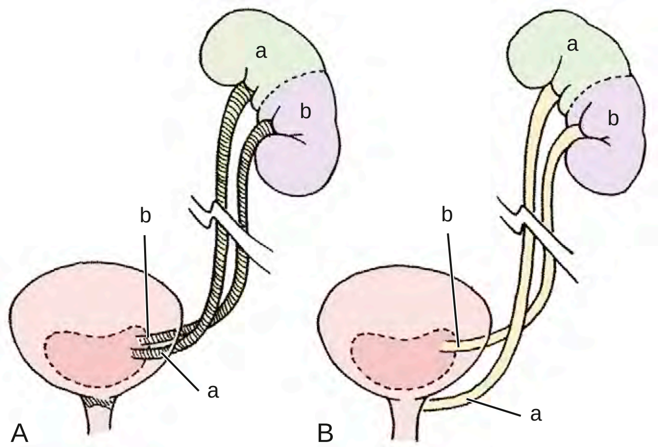

Figure 23-9 Illustration of the Weigert-Meyer rule. **A,** The ureter from the lower pole segment *(a)* of a complete duplication always enters the bladder cephalad to the ureter from the upper pole *(b)*. If there is reflux into only one segment, it would be to the lower pole because the ureterovesical junction tunnel is shorter. **B,** There would be reflux only to the upper pole of a complete duplication if both ureters are shifted caudad, so that now the upper pole ureter enters the bladder neck ectopically, without any normal ureterovesical junction valve mechanism *(b)*. The ureter from the lower pole is situated normally on the trigone and so does not reflux *(a)*.

When following children over many years with a lower grade of reflux into the lower pole of a complete duplication, resolution does occur, although it takes longer.[181,190] Husmann and Allen[190] showed a 10% resolution rate for grade II reflux in the completely duplicated system over 2 years, which is in contrast to reported rates of 20% to 30% resolution over 2 years for single systems. In their experience, breakthrough infection rates (17%) also were comparable to rates in single-system refluxers. Peppas and associates[191] noted that the mean age of resolution of low-grade (I to III) reflux with complete duplication was 4.4 years.

Periureteral Bladder Diverticulum

Congenital periureteral diverticula can occur in association with VUR. Diverticula seem to be larger in boys and of greater consequence. Amar[193] published a series of older boys with large diverticula and suggested that surgery would be necessary in all. It was thought that higher pressures of voiding in boys contributed to the lack of spontaneous resolution. It may be that the size of the diverticulum and the position relative to the ureteral orifice may be prognostic (Fig. 23-11). A large diverticulum with the ureter entering directly into it may have less chance of resolving than a smaller diverticulum that seems to involve less of the submucosal valve mechanism.

Spontaneous resolution of lower grade reflux with associated diverticula does occur. Afshar and coworkers[194] showed in a group of younger children (median age 3 years) that

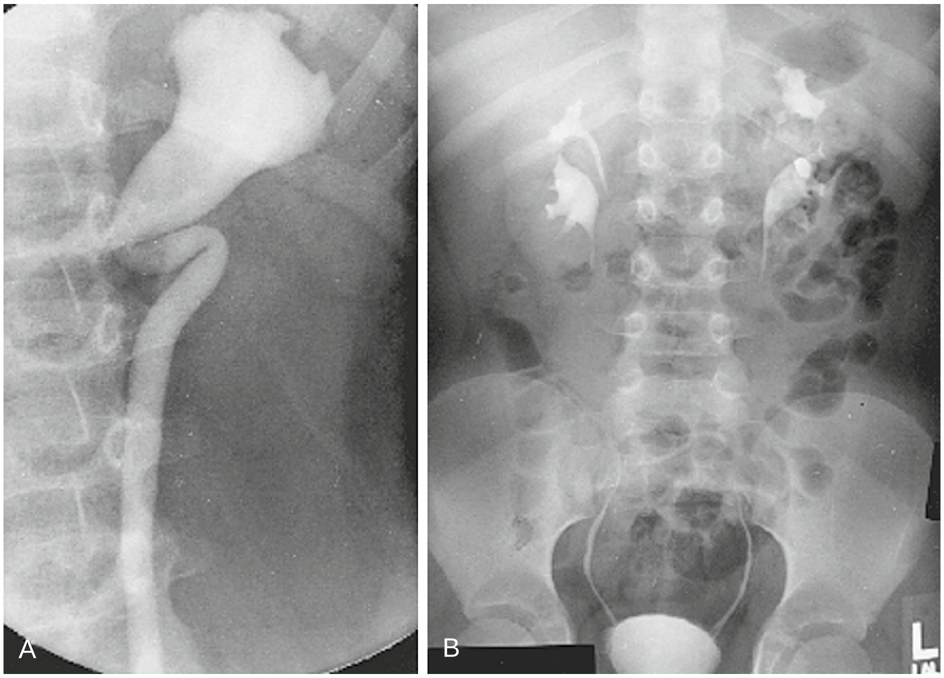

Figure 23-10 **A,** Contrast voiding cystourethrogram shows isolated vesicoureteral reflux into the upper pole of a complete duplication on the left. **B,** Intravenous pyelogram confirms duplicated systems bilaterally in this patient. At cystoscopy, the patient had an upper pole orifice ectopic to the bladder neck.

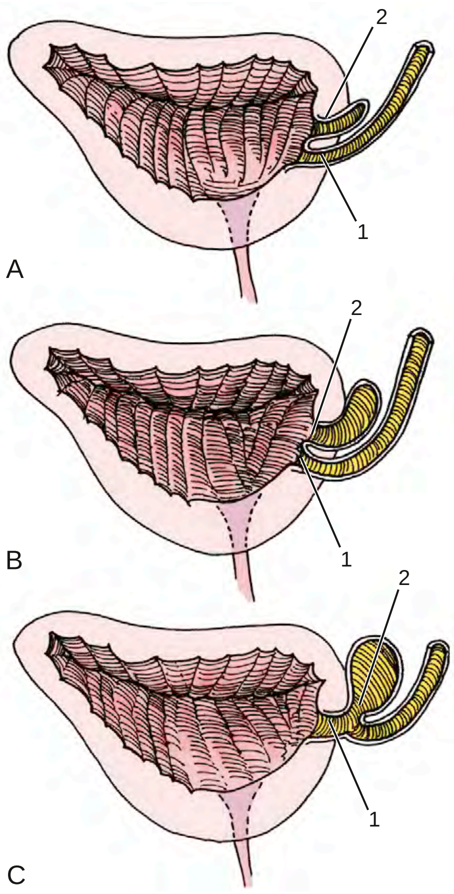

Figure 23-11 This sequence of drawings represents the anatomic variations of periureteral diverticula. **A,** In the mildest form, the ureterovesical junction is not disturbed. The ureteral orifice *(1)* enters the bladder near the diverticular orifice *(2)*. **B,** The second drawing portrays a moderately abnormal ureterovesical junction, wherein the valve may or may not function over time with growth of the child. The ureteral and diverticular orifices (*1* and *2*) are closer to each other. **C,** In the most severe form, the ureter enters the diverticulum itself, and the ureterovesical junction antireflux valve mechanism is entirely absent. At cystoscopy, only a single diverticular opening may be seen.

resolution rates were similar, grade for grade, to children without diverticula. Surgery was reserved for children with breakthrough infection, and 30% of patients ultimately underwent surgical correction. A trial of medical management is warranted for all patients with lower grades of reflux paraureteral diverticula, especially if the ureter does not directly enter the diverticulum. The ureterovesical valve mechanism can still become functional as it elongates with growth. Higher grades also may resolve spontaneously, but much less commonly.

Solitary Kidney

Palmer and colleagues[195] followed 21 patients with solitary kidneys and reflux. The etiologies of the absent kidneys were multicystic dysplastic kidney, renal agenesis, and ureteropelvic junction obstruction. Most with low-grade reflux were followed medically and resolved. The indication for surgery was mainly persistent high grade, and the investigators concluded that management strategies should be the same as those for two kidneys. Surgical correction is not absolutely indicated just because there is only one kidney.

Intrarenal Reflux

Intrarenal reflux was first documented in 1912.[196] It is rarely seen with contrast cystography, but has been shown in 14% of patients with severe scarring and in 7% of children with all grades of reflux.[196,197] Ransley and Risdon[197] showed that intrarenal reflux tends to occur in the polar regions owing to the presence of a concave papillary configuration that allows for the easy retrograde flow of fluid into the collecting system. Some authors believe that the presence of intrarenal reflux is an indication for reimplantation surgery, rather than observation on prophylaxis.[196] Rolleston and coworkers[198] observed that a large percentage of infants diagnosed early after infections had intrarenal reflux; many of these infants had scarred kidneys and seemed to develop new scars more easily with infection in these regions. Intrarenal reflux has rarely been observed in children older than 5 years.[199] There are few data, however, to show that the presence of intrarenal reflux is an absolute indication for the abandonment of a continuous prophylaxis regimen.

Reflux Diagnosed Antenatally or in Early Infancy

Prenatal ultrasound can detect dilation of the fetal renal pelvis. The most common postnatal finding in these children is VUR. Many children can have a normal postnatal ultrasound scan, and in one series more than half of the reflux identified was in children whose postnatal ultrasound scan showed no dilation.[103,200] Postnatal ultrasound correlates poorly with grade because minimal or even absent dilation can be associated with high-grade reflux.[201] Even if the prenatal hydronephrosis is mild, VUR can be present. Gloor and colleagues[202] found a 15% incidence of reflux in newborns whose renal pelves were less than 10 mm at 24 weeks' gestation.

Of reflux detected by prenatal ultrasound, 86% is in boys.[103,106,202,203] Most of these neonates have high-grade reflux, and 50% have scars seen on radionuclide scanning.[204,205] Boys tend to have more severe bilateral scarring, and these boys account for numerous children with reflux nephropathy and renal failure.[206] These scars are presumably due to dysplasia and not pyelonephritis because no postnatal UTIs had occurred before the imaging studies. Infants who start out with dysplastic-like scarring are also at high risk for further scarring owing to pyelonephritis.[207] These boys also have a higher incidence of breakthrough infection in the first 3 months of life compared with older boys with reflux.[206] It has been suggested that these boys undergo infant circumcision to reduce this incidence (see later discussion).[106] Cephalosporins or amoxicillin can be used for prophylaxis in early infancy. Patients can be switched to either nitrofurantoin or trimethoprim-sulfamethoxazole after 2 months of age.

Most prenatally detected reflux resolves. Brophy and colleagues[208] reported that 60% of a group of children with prenatally detected reflux resolved spontaneously after 2 years of follow-up. Upadhay and coworkers[209] reported a 52% resolution rate in a cohort after 4 years of observation. Arena and associates[205] observed that 81% of neonates with grades I to III reflux are resolved over a 15-year period. High resolution rates, especially for grades IV and V, have been reported in this age group.[210] Arima and associates[211] reported a 40% resolution rate for grade IV and a 38% resolution rate for grade V by 6 years of age. Scott[212] reported a 45% resolution rate of high-grade, prenatally detected reflux by 2 years of age. Gordon and associates[212a] reported a 35% resolution of prenatally detected reflux by age 2 years. Scott[212] also reported that some children whom he initially observed underwent surgery for increasing dilation with "gigantic reflux," and these individuals were probably those diagnosed early with megacystis-megaureter syndrome. The high resolution rates for grades IV and V reflux seen in children diagnosed prenatally are much greater than the rates seen in older children. In contrast, some series report a 0% resolution of grade V reflux in older children (see earlier).

Reflux diagnosed postnatally in early infancy also has a high resolution rate. These infants most often present with febrile UTI. As in the prenatally diagnosed group, most are boys, and many are high grade (grades IV and V).[213,214] Pinter and colleagues[215] reported that 80% of infants with grade II or III reflux had resolved by 8 years. Resolution rates of 30% to 40% for grades IV and V reflux diagnosed early in infancy secondary to a UTI have been reported.[213,216] Numerous (≤50%) infants diagnosed for the first time have scars, as in the prenatally detected group.[217] Of all male infants diagnosed after a febrile infection, 44% have Tc^{99m}-DMSA scans positive for scarring.[214] These children must be followed for hypertension and renal insufficiency, which can develop within 3 to 5 years of diagnosis, if there is considerable bilateral renal scarring.[217] Breakthrough infection in these children most often occurs with higher grades, and if there is associated voiding dysfunction.[218]

Voiding Habits and Voiding Dysfunction

Many clinicians incorporate changes in voiding habits along with antibiotic prophylaxis in a medical management regimen. Leiter[219] first suggested that scheduled voiding might be beneficial because it was reasoned that more reflux would occur at higher bladder volumes, and that intravesical tunnel length is shortened by bladder filling. Hutch[179] also speculated that double or triple voiding would help eliminate bacteria that had "returned" to the bladder from the upper tracts after an episode of reflux during the first void. Although these recommendations may play a role in medical management, their advantage has never been shown in large numbers of children.

More important has been the understanding that older, toilet-trained children with reflux and UTI may have certain aspects of voiding dysfunction.[153,220-223] Dysfunctional elimination syndromes, in which children are infrequent voiders and are constipated, are associated with an increased rate of UTI with and without reflux.[151] An increased rate of breakthrough infection in refluxing children on prophylaxis has been documented in these patients.[220,221] Dysfunctional voiding is more common in girls with reflux than in boys.[224] It is assumed that dysfunctional voiding is an acquired habit and of clinical significance only in older toilet-trained children.

Children with reflux do not have a higher incidence of voiding dysfunction than children without reflux. In a cohort of infants diagnosed with an infection and reflux before age 2 years and then followed, Shaikh and colleagues[225] showed that dysfunctional elimination syndromes are not more prevalent (approximately 20%) than in an age-matched control group without a history of infection and reflux. Similarly, Homayoon and coworkers[226] showed that the incidence of dysfunctional voiding in older children diagnosed with reflux during infancy was 20%. This incidence was not significantly different between low-grade and high-grade reflux groups, groups with and without renal scars, or groups with bilateral versus unilateral reflux.

Snodgrass[221] evaluated 128 boys and girls with reflux by assessing voiding dysfunction with a questionnaire, asking about voiding frequency and incontinence. There was a clear increase in the incidence of breakthrough UTIs in girls with a history of voiding dysfunction. Girls with a positive history had a 43% rate of breakthrough infection compared with 11% in girls without a positive history. Snodgrass[221] suggested placing girls with such a history on double prophylaxis. Koff and coworkers[222] came to a similar conclusion when looking at 143 children with reflux who were all old enough to be toilet trained. Breakthrough infections were four times more common in children with dysfunctional elimination syndromes. These authors also observed a longer time to spontaneous resolution in these children. Children with dysfunctional elimination syndromes had a higher rate of recurrent cystitis after disappearance of reflux. Finally, unsuccessful surgical outcomes were seen only in children with dysfunctional elimination syndromes. These authors recommended a regimen of frequent voiding, stool softeners, and laxatives, and anticholinergics.

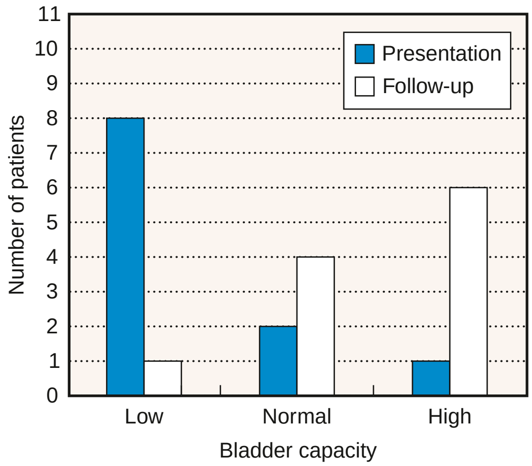

Figure 23-12 Evidence for changing and improving urodynamic parameters in infant boys diagnosed with high-grade vesicoureteral reflux. (From Sillen U, Bachelard M, Hermanson G, et al. Gross bilateral reflux in infants: gradual decrease of initial detrusor hypercontractility. *J Urol.* 1996;155:668.)

A voiding diary can be useful to the clinician in assessing dysfunctional elimination syndromes and for showing the problem to the family (Fig. 23-12). More recently, a validated questionnaire has been developed to assess for the presence of dysfunctional voiding—the dysfunctional voiding symptom score.[227] Children with higher scores have been shown to have lower rates of spontaneous resolution and higher rates of breakthrough infection on prophylaxis.

In a large study of more than 500 children with reflux, voiding dysfunction was noted to be a factor in the development of scars along with breakthrough infection.[156] Most of the 31 patients with new scars had voiding dysfunction. Significantly, 12 (42%) were 8 years or older, and 4 (13%) were older than 12 years. A voiding questionnaire was sent to the 310 children with grades III and IV reflux in the European arm of the IRS.[223] Of children, 18% had historical evidence of voiding dysfunction. More breakthrough infections were seen in the voiding dysfunction group, and there was a lower rate of spontaneous resolution in children with dysfunction who were medically managed on antibiotic prophylaxis.

Recognizing the prevalence of acquired habits of dysfunctional voiding in these children, McKenna and Herndon and their coworkers[228,229] suggested that many would benefit from biofeedback therapy. These authors believe that failure of the sphincter to relax appropriately is the primary problem (see later). Biofeedback therapy addresses the problem of dysfunctional sphincteric relaxation; bladder hypercontractility is believed to be secondary to this. Anticholinergics, although sometimes helpful in treating hypercontractility, may cause less efficient bladder emptying and more breakthrough infections, and should be used cautiously. A program of pelvic floor rehabilitation, using computerized animation programs in association with patch electrodes near the external sphincter, resulted in better bladder emptying and higher rates of spontaneous reflux resolution. The rate of surgical correction decreased by 90%.[229] Low-grade and high-grade reflux can resolve on this regimen, but it is more successful for grades I to III reflux.[229] Palmer and colleagues[230] also showed in an older group (mean age 9 years) of 25 girls with grades I and II reflux that intensive biofeedback therapy over 1 year resulted in a 55% resolution rate, without any intercurrent bladder infections.

Circumcision and Reflux

An increased rate of febrile UTIs in boys without VUR younger than 1 year old has been associated with not being circumcised.[231] Only two of the boys entered in the European arm of the IRSC were circumcised.[126] There were more boys with breakthrough infection and new scarring in the European arm as opposed to the North American arm.[128,129] There were almost no breakthrough infections in the European boys older than 1 year. Almost all of the boys from North America were circumcised, and there were fewer boys in the American arm of the study, suggesting that neonatal circumcision resulted in fewer infant boys presenting with infection in North America.

Thiruchelvam and Cuckow[232] found that circumcision reduced the incidence of recurrent infection in boys younger than 1 year old who had high-grade reflux. Conversely, Kwak and associates[233] did not find that performing circumcision at the time of reimplantation surgery reduced the incidence of postoperative infections. Those boys were older (mean age 42 months), however, and had their reflux corrected; one might not expect many postoperative infections, regardless of circumcision status. Cascio and associates[234] examined the flora from the periurethral area in uncircumcised boys with reflux (mean age 2.5 years), and found that there was an increase in pathogenic bacteria compared with cultures from a control group of uncircumcised boys without reflux (mean age 5.1 years). The pathogenic bacteria were most prevalent in infants younger than 1 year. They recommended circumcision in boys with high-grade bilateral reflux or unilateral reflux into a solitary kidney.

These data provide some support for the notion that circumcision may be beneficial in infant boys younger than 1 year with reflux and could be recommended along with placement on antibiotic prophylaxis.[235,236] This is not an absolute recommendation, however, and there are no prospective studies in large numbers of boys comparing the rates of breakthrough infection between boys who are and boys who are not circumcised.

Renal Failure and Hypertension

While the patient is under observation for spontaneous cessation, renal failure or hypertension may develop. The overall risk for renal failure owing to reflux is low—less than 1% for boys and 0.5% for girls.[237] When renal failure ensues in individuals with reflux, neither antibiotic prophylaxis nor reimplantation surgery can reverse it.[237-241] Most transplantation for reflux-related renal insufficiency occurs in young adults, but children 3 years old have required transplantation.[237] Gusmano and coworkers[241] reported the average age of onset of renal insufficiency to be 11 years. Most of these individuals have severe bilateral renal scarring.[240,242] Historically, reflux has been responsible for 30% of the pediatric end-stage renal disease population.[243] Between 1963-1982, 15% of all children with end-stage renal disease seen at the Royal Melbourne Hospital had reflux as an underlying cause.[244] Bailey and associates[245] reported that 11% of all children entering dialysis-transplantation programs in New Zealand between 1970-1992 had reflux.

The presence of proteinuria is the hallmark of progressive segmental glomerulosclerosis.[239,240] Renal failure and proteinuria can be found in individuals with one normal unscarred kidney, and the glomerular lesion has been documented in the contralateral unscarred renal unit.[246] Antibiotic prophylaxis may be continued as long as there is hope of spontaneous resolution. Surgery eliminates the need for prophylaxis, however, and reduces the likelihood of UTI after transplantation. The glomerular lesion does not recur in the transplanted kidney.[239,247]

Hypertension tends to develop during adolescence and young adulthood in children with renal scarring.[248] Normotensive adolescents may not develop high blood pressures until their 20s or 30s and require long-term follow-up. Generally, plasma renin levels gradually increase during adolescence in these individuals, but a normal early plasma renin level is not predictive of normal blood pressures when older.[248] Although most individuals with hypertension have extensive scarring, some have only minimal scarring, as seen on radionuclide scans.[242] Published reports from the 1960s and 1970s showed that pyelonephritic scarring was the cause of hypertension in 14% to 50% of children.[249,250] More recently, one pediatric hypertension clinic reported that reflux nephropathy was the most common underlying etiology, found in 40% of children seen.[251] Arar and colleagues[252] reported that reflux was the second most common cause of hypertension in a cohort of children gathered from 1987-1991.

Many individuals with severe end-stage nephropathy have no history of UTI.[237,253] This is especially true of boys with high-grade reflux. With the advent of prenatal ultrasound detection, it has been determined that many of these boys were born with high-grade reflux and severe bilateral renal dysplasia.[206] In the combined Australian and New Zealand Transplant registry, most boys and half of girls with reflux nephropathy had no history of infection. The assumption is that many had congenital dysplasia or asymptomatic infections. In a survey of children with end-stage renal disease in Italy, Marra and colleagues[254] found that 26% of all these children had reflux as a cause, and almost 80% were boys with high-grade reflux (grades IV or V). More than half of the boys were diagnosed before 6 months of age, and their mean age at time of renal failure was 3 years, suggesting that early diagnosis and corrective surgery cannot reverse the congenital dysplasia or course to renal failure in these boys. Girls presented with failure at a later age (mean 8 years), and most were diagnosed when older. Girls may have benefited more than boys from early detection and aggressive prevention of infection, reducing the incidence of acquired renal scarring.

Some reports have suggested that more widespread recognition and management of reflux may be reducing the rates of renal failure and hypertension in at-risk populations with reflux. The North American Pediatric Renal Transplant Cooperative Study[255] reviewed more than 3000 patients who received renal transplants between 1987-1995, and found that reflux nephropathy was present in only 5.7% of patients. Vallee and coworkers[256] reported the incidence of renal insufficiency and hypertension from a single pediatric referral center in a group of children accrued from 1982-1997. Six percent of renal disease patients and 4% of hypertensive patients had reflux. Only one patient had a history of UTI, suggesting that congenital renal dysplasia was responsible for most of the nephropathy. These rates of pediatric hypertension and end-stage renal disease attributed to reflux nephropathy are much lower than previously reported.

Craig and associates[257] showed that there has been no significant decrease in the rates of renal failure in children, as reported in the Australia and New Zealand Transplant registry. They examined the rates of end-stage renal disease secondary to reflux during the years 1971-1988, and assumed that reflux was more often diagnosed and treated in the more recent years. The overall incidence was unchanged (13.6%). Craig and associates[257] concluded that there was no evidence that recognition and treatment of reflux had any impact on the development of end-stage renal disease.

Reflux in the Renal Transplant Population

Reflux into the transplanted kidney has been implicated in an increased rate of pyelonephritis and diminished graft survival in only a small subset of children undergoing transplantation.[258-261] These children tend to be younger (<7 years old), and many have underlying voiding dysfunction secondary to neurogenic bladder or posterior urethral valves. Although graft loss because of reflux nephropathy alone is uncommon, classic renal scarring secondary to reflux has been shown in graft specimens, which have been removed for failure in children and adults.[262] The pyelonephritis can occur in boys and girls. Although medical management with long-term prophylaxis is possible in this group, the episodes of pyelonephritis are eliminated by reimplantation surgery.[258,259]

Ranchin and colleagues[263] suggested that prophylaxis alone may be sufficient. Reflux into transplanted kidneys in adults and older children with normal bladder function has not been associated with increasing episodes of UTI, pyelonephritis, or decreased graft survival.[247,264-267] In only one study is graft survival in adult transplant recipients less if reflux is present.[268] As mentioned previously, in children who were transplanted because of reflux nephropathy and focal segmental glomerulosclerosis, the glomerular disease does not recur in the transplanted kidney, even if it is also refluxing.[239,247] Neither antibiotic prophylaxis nor surgical reimplantation is necessary in most individuals who reflux into the transplanted kidney.

Reflux into the native kidneys of adults and children who have been transplanted also can be managed nonoperatively and without long-term antibiotic use.[269] Many of these individuals may have difficulty with recurrent cystitis, however, and they may benefit from reimplantation or require continuous prophylaxis.

Vesicoureteral Reflux and Pregnancy

Increased rates of pyelonephritis, toxemia, preterm delivery, fetal growth retardation, fetal loss, and decreased maternal renal function all have been reported in pregnant women with reflux alone and associated reflux nephropathy.[270-273] Fetal loss rates of 10% to 14% have been reported.[270,274] Many women with reflux are diagnosed for the first time as a result of an evaluation prompted by these problems during pregnancy.[274] In 137 women with reflux, El-Khatib and associates[275] found a 39% maternal complication rate consisting of UTI, pyelonephritis, preeclampsia, increasing creatinine and proteinuria, and renal stones. There were more serious complications in women with preexisting bilateral renal scarring and renal impairment.

Renal failure can be accelerated by pregnancy in women with preexisting renal insufficiency[274] Kincaid-Smith and Fairley[271] and Jungers and colleagues[273] found that most women with preeclampsia had decreased renal function because of severe reflux nephropathy at the outset of pregnancy. Maternal hypertension also was more prevalent, in their experience,[271] if there was proteinuria. Similarly, North and coworkers[276] found high rates of preeclampsia, increasing hypertension, deteriorating renal function, and increased rates of preterm delivery in women with known reflux and renal insufficiency. Preexisting hypertension or albuminuria further increased the risk of these complications.[276,277] Persistent reflux alone, without renal impairment, has been associated with more episodes of pyelonephritis, but not an increased rate of fetal loss.

Pyelonephritis also was the only major problem seen by Weaver and Craswell[270] as long as renal function was normal. Most of the fetal loss observed (14% of pregnancies) occurred in women with renal insufficiency.[273] In almost 20% of the patients in Weaver and Craswell's study,[270] UTI during pregnancy was the presenting feature that resulted in the diagnosis of reflux for the first time in these women.

Prophylaxis during pregnancy is possible, and drugs such as ampicillin and cephalosporins have been safely employed.[270] Most of the severe problems experienced by these women can be minimized, if not completely avoided, by prospective coordinated care.[273,274] Pregnancy is advised before significant elevations in serum creatinine if there is already bilateral renal scarring and renal insufficiency.

Is prior reimplantation protective of these women and fetuses? In Weaver and Craswell's small group experience,[270] women who had been reimplanted as children had no UTIs during pregnancy. Jungers and colleagues[273,274] found that pyelonephritis can occur in women with resolved reflux, but most occurred in women whose reflux was not corrected. They advised antireflux surgery in women before pregnancy, if there is a history of recurrent UTI.

Mansfield and coworkers[277] studied 62 pregnant women who had antireflux surgery during childhood and compared them with a cohort of 21 women who had a history of uncorrected reflux, but whose adult reflux status was unknown. There was a higher rate of UTI in the corrected group (40% overall; 18% pyelonephritis, 22% cystitis) than in the uncorrected group (1.3% pyelonephritis, 13.3% cystitis). These data are not entirely explained, but suggest that patients whose reflux was corrected as children may be more susceptible to infection. There was no information offered regarding the corrected group's incidence of renal scarring, reasons for reimplantation (e.g., breakthrough infection), or history of cystitis after reimplantation. The difficulty experienced by pregnant women with reflux is the reason that many pediatric urologists abandon medical management and suggest surgery if reflux does not resolve by adolescence in girls. Many of these girls will go on to have perinatal UTIs as women, despite having had their reflux corrected.

American Urologic Association Guidelines

No discussion of medical management of VUR can be complete without a summary of the effort by the American Urologic Association (AUA) to analyze the known data in an attempt to standardize treatment recommendations. This summary recapitulates much of what has been outlined in greater detail previously. The AUA published its guidelines for management in 1997.[278,279] As a result of meta-analysis of the literature, several conclusions were made incontrovertible by the data. Some of the guideline recommendations were the result of panel voting, however, when the data were less clear. Endoscopic therapy had not been approved for use in the United States

Table 23-8 Treatment Recommendations: Boys and Girls with Primary Vesicoureteral Reflux and with Renal Scarring

Clinical Presentation		Treatment					
		Initial (Antibiotic Prophylaxis or Open Surgical Repair)		Follow-up (Continued Antibiotic Prophylaxis, Cystography, or Open Surgical Repair[*])			
Reflux Grade/ Laterality	*Patient Age (yr)*	*Guideline*	*Preferred Option*	*Reasonable Alternative*	*Guideline*	*Preferred Option*	*No Consensus*[†]
I-II/unilateral or bilateral	<1	Antibiotic prophylaxis					Boys and girls
	1-5	Antibiotic prophylaxis					Boys and girls
	6-10	Antibiotic prophylaxis					Boys and girls
III-IV/unilateral	<1	Antibiotic prophylaxis			Girls: surgery if persistent	Boys: surgery if persistent	
	1-5	Antibiotic prophylaxis			Girls: surgery if persistent	Boys: surgery if persistent	
	6-10		Antibiotic prophylaxis		Surgery if persistent		
III-IV/bilateral	<1	Antibiotic prophylaxis			Surgery if persistent		
	1-5		Antibiotic prophylaxis	Surgery	Surgery if persistent		
	6-10	Surgery					
V/unilateral or bilateral	<1		Antibiotic prophylaxis	Surgery	Surgery if persistent		
	1-5	Bilateral: surgery	Unilateral: surgery			Surgery if persistent	
	6-10	Surgery					

[*] For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.

[†] No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.

From Elder JS, Peters CA, Arant BS Jr, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J Urol.* 1997;157:1846-1851.

and so was not considered an option. At present, the AUA is conducting a second literature review to update the guidelines.

In general, it was thought that medical and surgical management represented equally efficacious treatment options. The incidence of pyelonephritis seemed greater in cohorts of patients managed medically, whereas the incidence of cystitis was the same. There was no difference in the incidence of hypertension between medically and surgically managed groups. The AUA recommended measuring blood pressures periodically if renal scarring was present. Although early appropriate diagnosis and management of reflux could prevent uremia, it could not be reversed by reimplantation surgery or antibiotic prophylaxis. The AUA's review of the literature did not support the notion that surgical management achieved greater gains in somatic growth. They believed that the literature was unclear in the recommendations for girls and pregnancy. Although there was a high incidence of pyelonephritis in pregnant women who had undergone successful reimplantation surgery, the panel was not confident enough to state that girls should be allowed to enter adulthood without surgical correction, should spontaneous cessation not occur.

The AUA panel believed that all children with low-grade (I or II) reflux should be managed medically initially with continuous prophylaxis. The recommendations were less clear for grade III or IV reflux in older children (>4 years old), especially children with bilateral reflux, because rates of spontaneous resolution are lower. Grade V reflux could be watched in newborn and young infants, but had little likelihood of resolution in older children. The panel thought that there was more justification in choosing surgery over medical management in older children when there was higher grade bilateral reflux because the data suggest that spontaneous resolution may be less likely in those children (Tables 23-8 and 23-9).

Despite the reports of the association of voiding dysfunction and reflux, the panel did not recommend routine urodynamic testing, unless there was corroborating history. The panel believed that the benefit of anticholinergics in hastening the cessation of reflux, even with a history of voiding dysfunction, was questionable. Finally, despite the conclusions of the early investigators (discussed earlier) who observed children with reflux off of prophylaxis, they believed that intermittent prophylaxis had not been well studied. The idea of stopping prophylaxis after a certain age, recognizing that scar formation is less common in older children, has also not been

Table 23-9 **Treatment Recommendations: Boys and Girls with Primary Vesicoureteral Reflux and No Renal Scarring**

CLINICAL PRESENTATION		TREATMENT					
		INITIAL (ANTIBIOTIC PROPHYLAXIS OR OPEN SURGICAL REPAIR)		FOLLOW-UP (CONTINUED ANTIBIOTIC PROPHYLAXIS, CYSTOGRAPHY, OR OPEN SURGICAL REPAIR*)			
Reflux Grade/ Laterality	***Patient Age (yr)***	***Guideline***	***Preferred Option***	***Reasonable Alternative***	***Guideline***	***Preferred Option***	***No Consensus†***
I-II/unilateral or bilateral	<1	Antibiotic prophylaxis					Boys and girls
	1-5	Antibiotic prophylaxis					Boys and girls
	6-10	Antibiotic prophylaxis					Boys and girls
III-IV/ unilateral or bilateral	<1	Antibiotic prophylaxis			Bilateral: surgery if persistent	Unilateral: surgery if persistent	
	1-5	Unilateral: antibiotic prophylaxis	Bilateral: antibiotic prophylaxis				
	6-10		Unilateral: antibiotic prophylaxis	Bilateral: antibiotic prophylaxis		Surgery if persistent	
			Bilateral: surgery			Surgery if persistent	
V/unilateral or bilateral	<1		Antibiotic prophylaxis		Surgery if persistent		
	1-5		Bilateral: surgery	Bilateral: antibiotic prophylaxis	Surgery if persistent		
			Unilateral: antibiotic prophylaxis	Unilateral: surgery			
	6-10	Surgery					

*For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.
†No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.
From Elder JS, Peters CA, Arant BS Jr, et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J Urol.* 1997;157:1846-1851.

prospectively studied in large enough numbers to assess its safety. The AUA panel did not endorse this practice.

CONCLUSION

The major debate at the end of the 20th century was mainly between clinicians who advocated surgery for all children with reflux versus clinicians who advocated antibiotic prophylaxis. More recent innovations have changed the context of the debate, especially the approval of minimally invasive endoscopic therapy agents in the United States. More significant, however, is the challenging assertion that most children with reflux may not need treatment at all. No statistically valid, prospective, randomized studies conclusively show that all children with reflux benefit from treatment.

Wheeler and colleagues[133] published a meta-analysis of 10 randomized controlled trials, and concluded that it was uncertain that the identification of children with VUR was associated with a clinical benefit. The reasons are that the incidence of renal scarring is low in most children with low-grade reflux, subjecting many children to interventions that are unnecessary. In addition, the studies involved small numbers of patients. Craig and coworkers[257] showed that there has been no decrease in end-stage renal disease in Australia and New Zealand over the decades that VUR was allegedly more widely recognized and treated. This study seems to contradict the U.S. registry data, which show a clear decrease in incidence.[255] The assumption by Craig and coworkers[257] of treatment and recognition in the Southern Hemisphere may be inaccurate. In a contemporary Washington State report, 40% of infants hospitalized with a febrile urinary infection were not even evaluated for reflux, despite clear recommendations to do so by the American Academy of Pediatrics.[57] In a prospective study of 113 children with grades I to III reflux, Garin and associates[78] showed that the breakthrough infection and new scar rate was not reduced by continuous prophylaxis compared with controls on no medication. The age and sex of patient affected were not characterized, however, and most with recurrent pyelonephritis had grade III VUR.

North American pediatric urologists were surveyed about their indications for antireflux surgery. Most agreed that surgery would be performed for breakthrough infection, lack of compliance with a medical regimen, new renal scar formation while on prophylaxis, or grade V reflux in an older child.[177] Overall rates of surgery in populations of refluxers have infrequently been published and may not be comparable. Belman and Skoog[134] reported a surgical rate of 13% in a general population of children presenting with all grades. Greenfield and colleagues[144] reported a rate of 20% in a similar group. Koff and coworkers[222] reported a rate of 20% in older toilet-trained children with low-grade to intermediate-grade VUR.

Medical management is still employed for most children with VUR. This management consists of long-term antibiotic prophylaxis, periodic surveillance of urine cultures, and periodic VCUGs. Further study is necessary to define subpopulations of children who are at no or diminished risk of renal scarring. Perhaps these children can be discharged from prophylaxis and surveillance regimens altogether. Only large, statistically valid prospective studies of properly randomized patients can definitively answer these questions. At present, there is an ongoing National Institutes of Health–sponsored study comparing prophylaxis with placebo in children with grade I to IV reflux, which may provide some of these answers.[280] The development of a noninvasive means of diagnosing and following reflux to cessation without catheterization or radiation exposure would enhance compliance with long-term regimens considerably in patients who require therapy. An additional challenge is the diagnosis and prevention of prenatally established renal dysplasia in association with VUR, which, when present, cannot be altered by any form of medical or surgical postnatal care. These children account for most of the patients who suffer from the effects of reflux nephropathy in contemporary managed populations.

REFERENCES

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CHAPTER 24

ENDOSCOPIC TREATMENT OF VESICOURETERAL REFLUX

Prem Puri and Maria Menezes

Primary vesicoureteral reflux (VUR) is the most common urologic anomaly in children; it has been reported in 30% to 50% of children who present with a urinary tract infection.[1,2] The association of VUR, urinary tract infection, and renal damage is well known. Reflux nephropathy is the cause of end-stage renal failure in 3% to 25% of children and in 10% to 15% of adults.[3-5] The hereditary and familial nature of VUR is well recognized, and several studies have shown that siblings of children with VUR have a much higher incidence of reflux than the general pediatric population.[6] It also has been reported that when VUR is discovered in symptomatic siblings, it is usually of high grade and associated with a higher incidence of reflux nephropathy.[6]

The management of VUR in children has been controversial. Since the 1970s, there have been more than 5000 reports on this subject. Numerous studies have prospectively compared medical and surgical management of VUR. The Birmingham Reflux Study showed that more than half of the patients continued to show severe reflux after 5 years of medical treatment.[7] The study from Toronto showed that 93% of the patients with grade IV and 83% with grade III VUR had persistent reflux after 2 years of observational therapy, and 70% with grade IV and 50% with grade III VUR had persistent reflux after 5 years of this therapy.[8] The International Reflux Study Group in Children (European section) showed that 84% of the children with grade III and IV reflux randomly allocated to medical treatment still had reflux after 5 years.[9] In children with bilateral reflux, 91% had persistence of reflux after 5 years. In the European arm of the International Reflux Study at 10-year follow-up, only 52% of VUR resolved in children with grade III and IV reflux treated with antibiotic prophylaxis.[10] In children with bilateral grade III and IV reflux, it had resolved in only 39%.[10] The American Urological Association report on VUR reported a reflux resolution rate of 9.9% in bilateral grade IV VUR after 5 years of medical therapy.[11] All these studies showed further that observational therapy carries an ongoing risk of renal scarring. A question that is often asked in relation to these patients is how long should they be followed? Should they have antireflux surgery, or should they embark on a lifetime of chemoprophylaxis?

Several antireflux procedures have been described. Most entail opening the bladder and performing various procedures on the ureters. The two most popular operations are the Politano-Leadbetter technique of transvesical reimplantation of the ureters and the Cohen transtrigonal advancement of the ureters.[12] The principle behind antireflux procedures is to lengthen the intravesical ureter against a solid detrusor support to allow compression against the detrusor. Children undergoing these procedures spend several days in the hospital. These operations are effective, but not devoid of complications, even in the best hands.

In the report of the International Reflux Study Group, in the European section of the study, 19% of children had persistent VUR, and 5% had ureteral obstruction after antireflux surgery.[13] In the American section of the study, there was no obstruction, but 9% had persistent postoperative VUR. Surgery in children with high-grade reflux with dilated ureters carries a higher rate of failure and morbidity than surgery in children with lower grade reflux and nondilated ureters. The American Urological Association report on VUR reported persistence of VUR in 19.3% of ureters after reimplantation of ureters for grade V reflux.[11] The rate of obstruction after ureteral reimplantation needing reoperation reported by the American Urological Association in 33 studies was 0.3% to 9.1%.[11]

Since its first experimental description in 1984 in piglets,[14] endoscopic correction of VUR has proved to be a highly successful, minimally invasive treatment for this condition.[15-22] Several tissue-augmenting substances have been used for subureteral injections, such as polytetrafluoroethylene (PTFE) (Teflon), collagen, silicone (Macroplastique), autologous chondrocytes, calcium hydroxyapatite, and dextranomer/hyaluronic acid (Dx/HA) copolymer (Deflux). Excellent long-term results have been reported with subureteral Teflon injections (STING procedure).[16,17] Some groups have been concerned, however, with the use of PTFE as an implant material because of reported distant particle migration after periurethral, periureteral, and intravenous injection in animal studies, despite the reported evidence that the minimal quantities of paste used to correct VUR and the location of the injection away from major vessels is not associated with particle migration.[23-25]

In 2001, Deflux was approved by the U.S. Food and Drug Administration (FDA) as an acceptable tissue-augmenting substance for subureteral injection therapy for VUR. Since then, endoscopic treatment has become increasingly popular for managing VUR, and Deflux is the most widely used tissue-augmenting substance. Endoscopic treatment has several advantages. In contrast to long-term antibiotic prophylaxis, it offers immediate cure of reflux at a high incidence, its success does not rely on patient or parent compliance, and the procedure is virtually free of adverse side effects. Long-term administration of antibiotics implies the danger of bacterial resistance with promotion of breakthrough urinary tract infections, and antibiotics are usually needed for years.

In a long-term study, Schwab and coworkers[26] reported spontaneous resolution rates of 13% yearly for grade I to III reflux and only 5% for grade IV to V reflux. Median time to resolution under antibiotic treatment was 4.5 years for grade III and 9.5 years for grade IV reflux. Overall resolution rates were 83.3% for grade I to 35.5% for grade IV reflux. In their study in infants with grade IV and V reflux, Sjostrom and colleagues[27] noted a spontaneous resolution rate of 29% in boys and 4% in girls in the first year and thereafter an annual resolution rate of only 9% for boys and girls. Despite antibiotic prophylaxis, 50% of children had breakthrough urinary tract infections, primarily in the infant year, and more frequently in girls than in boys.[27] The high incidence of breakthrough urinary tract infection in boys can be attributed to uncircumcised boys typical in European cohorts, but does not explain the high incidence of urinary tract infection in girls. A randomized study comparing antibiotic prophylaxis with endoscopic treatment with Dx/HA copolymer showed a 69% success rate for endoscopic treatment versus 38% for antibiotic prophylaxis after 1 year of treatment.[20]

The various advantages of endoscopic treatment do not remain unnoticed by the general population. A more recent study showed that 80% of parents prefer endoscopic treatment to antibiotic prophylaxis and open surgery when given a free choice after detailed information about all three treatment options.[28] Another study from Washington showed that parents of children with VUR preferred antibiotic treatment as the initial treatment, but if long-term prophylaxis was required, they preferred definitive correction, and in particular endoscopic treatment because it was less invasive.[29]

TISSUE-AUGMENTING SUBSTANCES FOR ENDOSCOPIC INJECTION

Dextranomer/Hyaluronic Acid Copolymer

The tissue-augmenting substance most commonly used for subureteral injection is Dx/HA copolymer (Deflux), which consists of microspheres of dextranomer in 1% high-molecular-weight sodium hyaluronan solution.[18] Each 1 mL of Deflux contains 0.5 mL of sodium hyaluronan and 0.5 mL of dextranomer. Deflux is biodegradable, is nonimmunogenic, and has no potential for malignant transformation. The dextran microspheres (80 to 250 μm in diameter) are made from cross-linked dextran polymers with a network configuration. This network acts as a carrier that recruits cells from the surrounding tissues. Histopathologic examination after the injection of Deflux has shown giant cells between the dextran microspheres, with an ingrowth of fibroblasts and vessels, and the production of varied amounts of collagen around the dextranomers. There is a loss of volume of 25% during the first year after injection. In recent years, several studies have reported safety and effectiveness of the endoscopic treatment of VUR using Deflux as a tissue-augmenting substance.[19-22,30-34]

Polytetrafluoroethylene

Currently, PTFE (Teflon) is one of the most widely used biomaterials in surgery. It belongs to a family of polymers, substances composed of large molecules formed by chemical combinations of many small ones (monomers) into chains or networks. PTFE is the best-known fluorocarbon polymer and is probably the most inert of the plastic materials. It has the lowest coefficient of friction and is highly crystalline (>94% crystallinity). The polymer has a high molecular weight, high density (2.15 to 2.2 g/mL), low tensile strength (17 to 28 MPa), and a low surface tension (18.5 erg/cm^2). Teflon is considered to be relatively inert chemically, is easily sterilized, and retains its functional characteristics for long periods. PTFE is usually not rejected by the host and has not been found to cause any malignancies in humans. Medical applications include (1) vascular grafts when fabricated into textiles; (2) knitted fabrics for the treatment of aneurysms; (3) heart valves and aortic implants; (4) shunts in hemodialysis equipment; (5) bone, cartilage, and ligament replacements; and (6) sutures and tissue replacement patches.

PTFE paste is a suspension of biologically inert PTFE particles in glycerin. The glycerin is 50% of the paste by weight. After injection, the glycerin is absorbed into the tissues, and the PTFE implant achieves a firm consistency, retaining its shape and position at the injection site, and is encapsulated by thin fibrous tissue.[14] PTFE paste has been used in clinical medicine for more than 35 years with little morbidity.[35-42] Politano and colleagues[37-41] pioneered periurethral injections of PTFE for urinary incontinence in 1964, and since then the procedure has been performed in hundreds of patients with little morbidity. Similarly, no significant complications have been reported with the endoscopic treatment of VUR with PTFE paste in several thousands of patients since 1984.[15,43-111]

Cross-Linked Bovine Collagen

Several investigators have used bovine collagen cross-linked with glutaraldehyde as the main alternative to PTFE. It was widely used previously to produce cardiac valves and hemostatic agents and sutures, and as a soft tissue substitute. Cross-linked bovine collagen represents a soluble and purified preparation of bovine collagen that is stabilized further by the addition of 0.0075% glutaraldehyde to effect fibril cross-linking. It causes minimal tissue reaction locally when injected and is easily injectable through a 25-gauge needle with standard endoscopic equipment. Initially, in short-term studies, collagen seemed promising for the correction of low-grade reflux.[112-114] Long-term studies have shown, however, that collagen is not an ideal tissue-augmenting substance.[115-118] It has a documented tendency to disappear with time, resulting in the recurrence of reflux.

Polydimethylsiloxane

Polydimethylsiloxane (Macroplastique) has been used as a tissue-augmenting substance for the endoscopic correction of VUR.[119-121] The silicone paste is made of 40% solid textured polydimethylsiloxane particles suspended in 60% hydrogel. Its physical properties are similar to those of PTFE. There are no long-term follow-up studies available, however, with this injectable substance for the treatment of VUR. Distant silicone particle migration has also been reported after periurethral and periureteral microparticulate silicone injections. Buckley and coworkers[122] found that small silicone particles migrated to the lungs, kidneys, brain, and lymph nodes 4 months after injection into mongrel dogs. Henly and coworkers[123] confirmed these results after periurethral injection of particles less than 70 μm in female dogs.

Autologous Chondrocytes

In 1999, Diamond and Caldamone[124] reported preliminary results of endoscopic injection of autologous chondrocytes to correct VUR in children. Because chondrocytes possess the ability to form viable cartilage, they have good potential as a stable tissue-augmenting substance. Twenty-nine children (46 ureters) with grades II to IV VUR were treated. Each child underwent cystoscopy and ear cartilage biopsy at the initial setting. Chondrocytes were grown in culture for 6 weeks. Patients underwent subureteral endoscopic injection of autologous chondrocytes. Ultrasonography was performed at 1 month, and radionuclide cystography was done 3 months postoperatively to confirm reflux resolution. When reflux persisted, repeat treatment with stored chondrocytes was offered. Initial chondrocyte injection corrected reflux in 26 of the 46 ureters (57%), whereas secondary injection was successful in 12 of 19 in whom the first injection did not work (63%). Overall reflux was corrected in 38 of the 46 ureters (83%) and in 24 of the 29 patients (83%). There were no significant complications. In another more recent study, reflux resolved after one chondrocyte injection in 61% in the early follow-up group and 74% in the late follow-up group.[125] The potential advantages of autologous chondrocyte injection include a sustained antireflux effect from viable

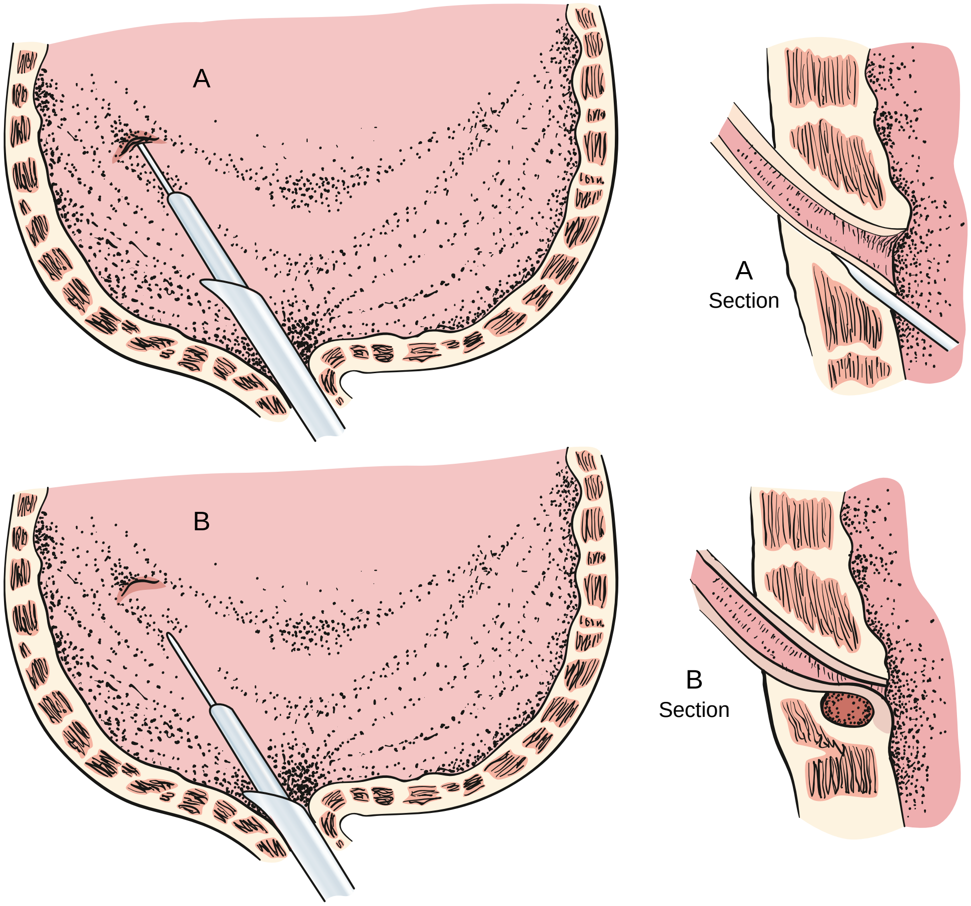

Figure 24-1 **A,** Needle is introduced under the bladder mucosa, 2 to 3 mm below the affected ureteral orifice at the 6 o'clock position. The needle is advanced about 3 to 4 mm into the lamina propria, and the injection is started slowly. **B,** Correctly placed implant creates a slitlike ureteric orifice. In children with grade IV or V reflux, the needle should be inserted directly into the affected ureteral orifice, and the injection should be made under the mucosa.

chondrocytes, and prevention of bioincompatibility owing to their autologous nature.

Calcium Hydroxyapatite

Synthetic calcium hydroxyapatite is a sterile apyrogenic injectable slurry of spherical particles in an aqueous-based gel carrier. The particles are spherical in shape and range from 75 to 125 µm in diameter. Calcium hydroxyapatite provides long-term bulking with anticipated 25% volume loss. In a multicenter study using calcium hydroxyapatite for endoscopic correction of VUR, only 46% of ureters were cured at 1-year follow-up. The primary center at Rochester achieved a 2-year cure rate in 72% of ureters.[126]

TECHNIQUE OF SUBURETERAL INJECTION

The indications for endoscopic correction of VUR are the same as for open antireflux operations. It is generally agreed that lesser grades of reflux (grade I or II international classification) can be managed conservatively. Grade II reflux is conservatively managed unless there are "breakthrough infections" while on antimicrobial therapy, or poor compliance on medical management. Children with grades III to V VUR are generally considered candidates for endoscopic correction. In addition to primary VUR, the endoscopic procedure has been used successfully to treat VUR in duplex system, VUR secondary to neuropathic bladder and posterior urethral valves, VUR in failed reimplanted bladders, and VUR into ureteral stumps.

The technique of endoscopic injection of Deflux paste or any other tissue-augmenting substance is simple and straightforward. The disposable Puri catheter for injection (Storz) is a 4F nylon catheter onto which is swaged a 21-gauge needle, with 1 cm of the needle protruding from the catheter. Alternatively, a rigid needle can be used. A 1-mL syringe prefilled with Deflux is attached to the injection catheter. All cystoscopes available for infants and children can be used for this procedure. The injection catheter can be introduced through a 9.5F, 11F, or 14F cystoscope.

The patient should be placed in the lithotomy position. The cystoscope is passed, and the bladder wall, trigone, bladder neck, and both ureteric orifices are inspected. The bladder should be almost empty before proceeding with the injection because this helps to keep the ureteric orifice flat rather than away in a lateral part of the field. The injection of Deflux should not begin until the operator has a clear view all around the ureteric orifice. Under direct vision through the cystoscope, the needle is introduced under the bladder mucosa, 2 to 3 mm below the affected ureteral orifice at the 6 o'clock position (Fig. 24-1). In children with grade IV and V reflux with wide ureteric orifices, the needle should be inserted not below, but directly into the affected ureteral orifice. It is important to introduce the needle with pinpoint accuracy. Perforation of

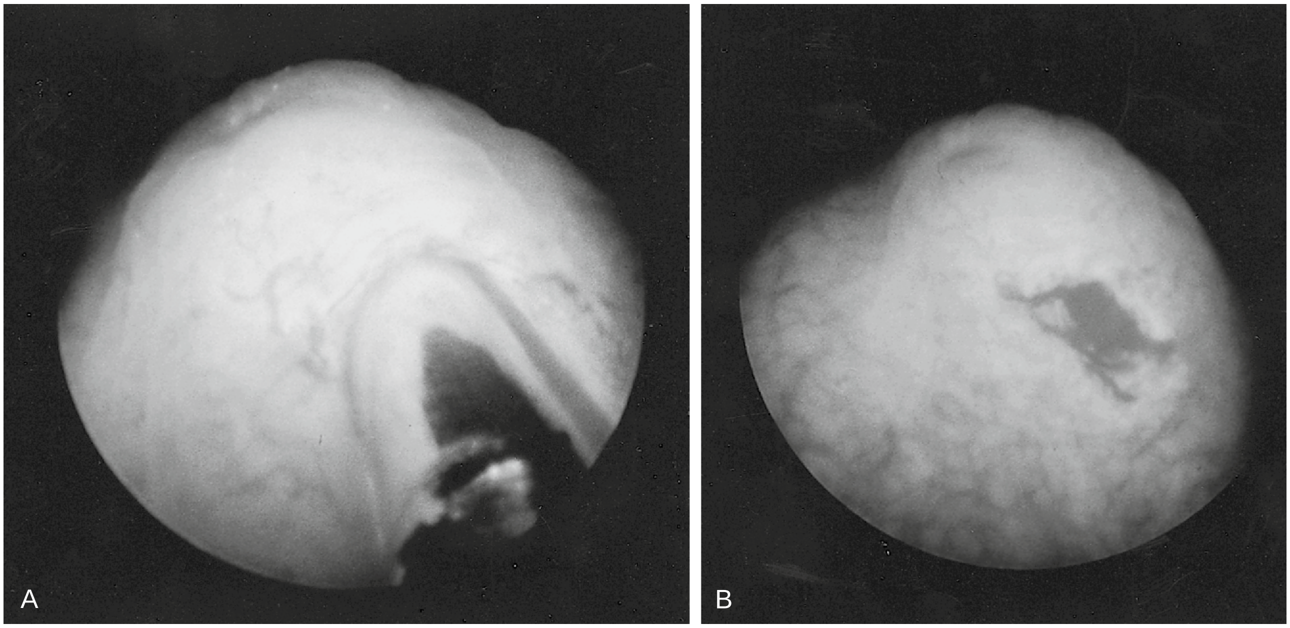

Figure 24-2 Endoscopic appearance of subureteral injection. **A,** Injection in progress. **B,** Correctly placed implant gives an appearance of a nipple on the top of which is a slitlike orifice.

the mucosa or the ureter may allow the paste to escape and may result in failure.

The needle is advanced about 4 to 5 mm into the lamina propria in the submucosal portion of the ureter, and the injection is started slowly. As the paste is injected, a bulge appears in the floor of the submucosal ureter. During the injection, the needle is slowly withdrawn until a "volcanic" bulge of the paste is seen. The needle should be kept in position for 30 to 60 seconds after injection to avoid extrusion. Most refluxing ureters require 0.2 to 0.6 mL of Deflux to correct reflux. A correctly placed injection creates the appearance of a nipple on the top of which is a slitlike or inverted crescent orifice (Fig. 24-2). If the bulge appears in an incorrect place, the needle should not be withdrawn, but should be moved so that the point is in a more favorable position. The noninjected ureteric roof retains its compliance, while preventing reflux. The success or failure of the procedure depends on the accuracy of the injection technique.

Most patients are treated as outpatient cases. Antibiotic prophylaxis is prescribed for 12 weeks after the procedure. Micturating cystography and renal ultrasonography are performed 3 months after discharge. Follow-up renal and bladder ultrasound scans are obtained 12 months after endoscopic correction of reflux and then every 2 years to monitor the growth of kidneys and the size of the subureteral implant.

RESULTS OF ENDOSCOPIC TREATMENT OF VESICOURETERAL REFLUX WITH DEFLUX

In 2001, the FDA approved Dx/HA copolymer (Deflux; Q-Med Scandinavia, Uppsala, Sweden) as an acceptable implant for subureteral injection of VUR in children. Puri and colleagues[31] prospectively evaluated the effectiveness of Deflux as first-line treatment for high-grade VUR. Between 2001 and 2004, 692 children with a median age of 2.1 years with high-grade VUR underwent endoscopic subureteral injection of Deflux at our institution. VUR was unilateral in 283 patients and bilateral in 409. Of the 1101 ureters, VUR was grade II in 35 (3.2%), grade III in 580 (52.7%), grade IV in 457 (41.5%), and grade V in 29 (2.6%). Reflux resolved after first, second, and third endoscopic Deflux injections in 952 (86.5%), 130 (11.8%), and 19 (1.7%) ureters (Table 24-1).[31] Eighteen ureters (2.6%) had symptomatic urinary tract infections during follow-up, and reflux recurred in 2 ureters (0.2%).

Table 24-1 **Vesicoureteral Reflux (VUR) Resolution after Endoscopic Treatment with Deflux**

VUR	One Injection	Two Injections	Three Injections	Total
Grade II	35 (100%)	0	0	35
Grade III	540 (93.1%)	36 (6.2%)	4 (0.7%)	580
Grade IV	355 (77.7%)	87 (19%)	15 (3.3%)	457
Grade V	22 (75.9%)	7 (24.1%)	0	29
Total	952	130	19	1101

Other studies have shown good results with the use of Deflux. Lavelle and associates[32] showed success rates of 82%, 84%, 78%, and 73% for grades I, II, III, and IV VUR. They found that mound morphology was the only statistically significant predictor of a successful outcome. Kirsch and colleagues[21] found a cure rate of 90% for grade I, 82% for grade II, 73% for grade III, and 65% for grade IV VUR. There were no statistically significant differences in age, grade, volume injected, bilaterality, or gender. The same authors showed improved results with submucosal implantation within the intramural ureter using hydrodistention technique.[127] Other tissue-augmenting substances, such as polydimethylsiloxane, have shown an 81% overall VUR correction rate with a single injection, with no surgical complications.[128] A study from Austria showed that reflux correction using Macroplastique was 80.9% and using Deflux was 67.6% at 1-year follow-up.[30]

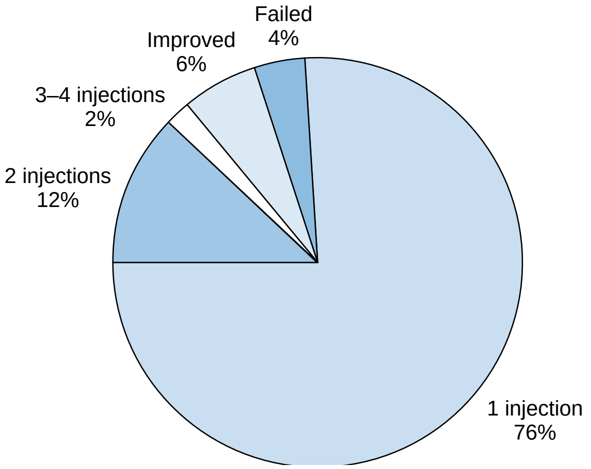

Figure 24-3 Results of subureteric Teflon injection (STING) in 12,251 refluxing ureters.

In a meta-analysis on endoscopic therapy for VUR, the database included 5527 patients.[129] After one treatment, the reflux resolution rate for grades I and II reflux was 78.5%, for grade III was 72%, for grade IV was 63%, and for grade V was 51%. If the first injection was unsuccessful, second treatment had a success rate of 68%, and the success rate of a third treatment was 34%.

LONG-TERM RESULTS

Numerous multicenter studies of STING have been reported in the literature.[54,71,88] All these studies have shown that STING is a simple outpatient procedure, effective in correcting all grades of VUR, and is associated with little morbidity.

In 1998, Puri and Granata[54] reported the results of a multicenter survey of endoscopic treatment of VUR using PTFE paste in 8332 children. Fifty-three pediatric urologists and pediatric surgeons at 41 centers worldwide answered an inquiry regarding experience with STING in VUR. Data were collected from a completed standard questionnaire. From 1984 to 1996, 1921 boys and 6411 girls with a mean age of 4.5 years (12,251 refluxing ureters) were treated endoscopically with STING. Reflux was grade I in 407 (3.3%), grade II in 3832 (31.2%), grade III in 5213 (42.5%), grade IV in 2218 (18.1%), and grade V in 581 (4.7%) ureters. In most patients, STING was performed on an outpatient basis. Most urologists monitored patients with voiding cystourethrography and renal ultrasonography at 3 months, 1 year, and 3 years. All patients were followed for 1 to 13 years.

Reflux resolved in 9226 ureters (75.3%) after one PTFE injection, in 1478 (12%) after two injections, and in 250 (2%) after three or four injections (Fig. 24-3). VUR improved to grade I after one or two injections in 743 (6%) ureters, which needed no further treatment. Subureteral injection failed to correct reflux in 554 ureters (4.5%), which were then treated with ureteral reimplantation. Vesicoureteral junction obstruction requiring ureteral reimplantation developed in 41 ureters (0.33%). More than 90% of ureters have been followed for more than 2 years. At follow-up, reflux recurred in 326 (2.8%) endoscopically corrected refluxing ureters. No clinically untoward effects were reported in any patient because of the use of PTFE as an injectable material.

A more recent prospective multicenter trial in the United States using synthetic calcium hydroxyapatite for endoscopic treatment of VUR showed 46% and 40% ureteral cure rates at 1 and 2 years.[126] Synthetic calcium hydroxyapatite was found to be safe, durable, and effective.

During the 6-year period from 1984 to 1990, we used the STING procedure to treat 258 children with primary VUR at the National Children's Hospital in Dublin. These patients have been followed for 10 to 17 years. There were 205 girls and 53 boys 3 months to 14 years old (mean age 5.1 years). Of patients, 92 had unilateral reflux, 129 had bilateral reflux, and 37 had refluxing duplex systems (6 of these bilateral). The indication for STING was high-grade reflux (grades III to V); patients with low-grade reflux and with scarring on radionuclide scanning and recurrent urinary tract infections while on chemoprophylaxis also were treated. Ninety-six percent of ureters had grade III to V reflux. Reflux was corrected in 302 ureters (76.8%) after a single injection of PTFE paste. Of these 302 ureters, 87% required less than 0.3 mL of paste per ureter to stop the reflux. The procedure failed in only seven ureters (seven patients), and these required reimplantation.

Ninety-seven percent of the patients were discharged from the hospital on the day of the procedure. A procedure-related complication occurred in only one patient, who was readmitted to the hospital with unilateral ureteral obstruction the day after a bilateral STING for grade IV reflux. She required a ureteral catheter for 5 days while the edema subsided. Follow-up micturating cystography and ultrasonography 9 years later showed no reflux or obstruction in this child. At the time of follow-up, 4 of the 251 children were lost to follow-up, or their parents refused to let the children have further cystography. The remaining 247 were followed for 10 to 16 years. Follow-up micturating cystography in these 247 patients with 379 refluxing ureters showed that 361 ureters (95.3%) remained free from VUR; there was recurrence of VUR in only 18 ureters (4.7%). Of these 18 ureters, 11 showed grade I or II reflux, and no further treatment was given. The seven remaining ureters had grade II or grade IV reflux and were reinjected without any difficulty. No untoward effects were seen in any of these children that were attributable to the use of PTFE as the injectable material.

Other investigators have shown favorable results of endoscopic correction of VUR at long-term follow-up. Lackgren and coworkers[19] showed a correction in 68% of ureters at long-term follow-up, using Deflux as the tissue-augmenting substance.[19] Only 12% of patients were referred for open surgery. Capozza and colleagues[130] had a 77% success rate at long-term follow-up after endoscopic correction of high-grade VUR.

Although endoscopic treatment provides a high rate of success in children with grades II to IV VUR, its role in the management of grade V reflux has been questioned. We reviewed our 21-year experience of endoscopic treatment in children with grade V primary VUR. During 1984 to 2004, 132 children (166 ureters) with grade V primary VUR underwent endoscopic treatment at our hospital.[131] These patients were followed for a median of 12.2 years (range 1 to 21 years). VUR was completely resolved after first injection in 88 (53%) ureters and downgraded to grade I or II in 26 (15.7%), requiring no further treatment. VUR resolved after a second and third injection in 36 (21.7%) and 10 (6%) ureters (Table 24-2). Endoscopic treatment failed to correct VUR in six (3.6%) ureters, requiring ureteral reimplantation in five and nephrectomy in one. During the follow-up period, 13 patients developed urinary tract infections, and on investigation recurrence of VUR was noted in 7 patients (9 ureters, 5 high-grade VUR, 4 low-grade VUR). All recurrences occurred within 3 years of the initial treatment. No injection-related morbidity or

Table 24-2 Results of Endoscopic Treatment in Grade V Primary Vesicoureteral Reflux (VUR) (*N* = 166)

Results	No.
VUR resolved after single injection	88 (53%)
VUR downgraded to grade I or II after first injection	26 (15.7%)
VUR resolved after two injections	36 (21.7%)
VUR resolved after three injections	10 (6%)
Failure	6 (3.6%)

Table 24-3 Vesicoureteral Reflux (VUR) Resolution for Each Reflux Grade in 467 Refluxing Ureters in Infants

VUR	One Injection	Two Injections	Three Injections	Total
Grade II	14 (100%)	0	0	14
Grade III	175 (93.1%)	12 (6.4%)	1 (0.5%)	188
Grade IV	194 (78.2%)	48 (19.4%)	6 (2.4%)	248
Grade V	11 (64.7%)	5 (29.4%)	1 (5.9%)	17
Total	394	65	8	467

untoward effects from the tissue-augmenting substances were noted in any patient.

ENDOSCOPIC CORRECTION OF VESICOURETERAL REFLUX IN SPECIAL SITUATIONS

Duplex Systems

VUR is one of the most common problems associated with duplex systems.[132] Spontaneous resolution of VUR in these patients is low because the anatomic configuration of the region prevents the development of the submucosal tunnel, and until more recently, the presence of VUR, especially high-grade reflux, has been an indication for open surgical correction.[133-135] STING has been used successfully to treat VUR in duplex systems.[86,88,136,137]

With an incomplete duplex system, the procedure is as described for a single system. In the case of a complete ureteral duplication, the needle is introduced 2 to 3 mm below the *lower* ureteral orifice at the 6 o'clock position, but the entire length of the needle (8 mm) is advanced behind the two ureters. During the injection, the needle is removed slowly until the bulge of paste is seen, and the *two* orifices become slitlike.

In a study from our institution, 87 children with VUR into duplex systems underwent endoscopic subureteral injection of Deflux.[137] Duplex system was unilateral in 80 and bilateral in 7, resulting in 94 refluxing units. The reflux was into the lower moiety in 50, upper moiety in 5, and upper and lower moieties in 39. The reflux was grade II in 2, grade III in 45, grade IV in 41, and grade V in 6 ureters. There was complete resolution of VUR in 72 (76.6%) ureters after one injection. For the correction of VUR, 20 ureters (21.3%) required two injections, and 2 (2.1%) required a third injection. Follow-up ultrasound scans at 3 months to 6 years later showed no evidence of delayed subureteral obstruction.

Other series have shown similar results, with more than two thirds showing complete resolution, and almost 90% showing improvement in the degree of reflux after one injection of PTFE in complete duplicated systems after a follow-up of 2 years.[86,88] In this difficult group of patients, STING can resolve reflux in most cases, and we now recommend STING rather than open surgery as the first-line treatment.

Over the last 21 years, 109 children have undergone endoscopic puncture of ureterocele, which manifested as part of duplex systems in 97 and a single system in 12. Spontaneous resolution of VUR after successful puncture of the ureterocele was seen in 42% of renal refluxing units (RRUs). Endoscopic correction was undertaken in 33 RRUs with VUR into the lower moiety of the ureterocele kidney and 11 renal RRUs of the contralateral kidney. Reflux was corrected in 31 (70%) of the 44 RRUs after a single injection and resolved after a second injection in another 9 (21%). In four (9%) RRUs, endoscopic correction failed, and the patients underwent open reimplantation. Our data showed that endoscopic treatment of VUR associated with ureterocele is a simple, effective, and safe procedure.[138]

Infant Vesicoureteral Reflux

Between 1985 and 2004, 411 infants underwent endoscopic treatment of grades III to V VUR at our hospital. Of these, 382 were available for follow-up. Complete resolution of VUR after a single injection occurred in 443 ureters (69%), including 73% with Deflux and 65% with PTFE. Of the 642 ureters, 127 (20%) required more than one injection to correct VUR. In 60 ureters, VUR was downgraded to grade I or II, and no further treatment was given. Open surgical correction was required in 12 ureters. This study shows that endoscopic treatment in infant VUR is safe and effective, and may provide protection from reflux-associated renal damage.[139]

To evaluate prospectively the effectiveness and safety of Dx/HA copolymer in treating infants with VUR, 276 infants underwent endoscopic treatment of VUR with Deflux at our institute.[33] VUR resolved completely in 79.9% of ureters after a single injection and was downgraded to grade I in 4.4% (Table 24-3). A second injection was required in 14% and a third injection was required in 1.7% for resolution of VUR. Three children developed urinary infections during the follow-up period, and one of them was found to have recurrence of VUR on investigations. VUR resolution after endoscopic injection was found to decrease with increasing VUR grade.

Vesicoureteral Reflux in the Neuropathic Bladder

VUR is a major cause of morbidity in children with a neuropathic bladder. Reflux can be partially controlled by bladder decompression procedures, such as vesicostomy, catheter drainage, and bladder neck resection, but despite these procedures, the reflux rarely resolves spontaneously. Also, ureteral reimplantation that is almost universally successful in primary VUR is more difficult in the thick-walled trabeculated neuropathic bladder. STING would seem to be a good alternative. STING is not as straightforward in the neuropathic bladder as it is in primary VUR. These children always must be protected with prophylactic antibiotics because the neuropathic bladder is always potentially infected. Most ureteral orifices in the neuropathic bladder are described as patulous; however, in every series, there are numerous cases in which STING has been impossible because the orifices cannot be identified owing to the severe trabeculation.[46,49,52,61-64,85,87,111]

In common with the treatment of primary VUR, most children (85%) with VUR in a neuropathic bladder can be

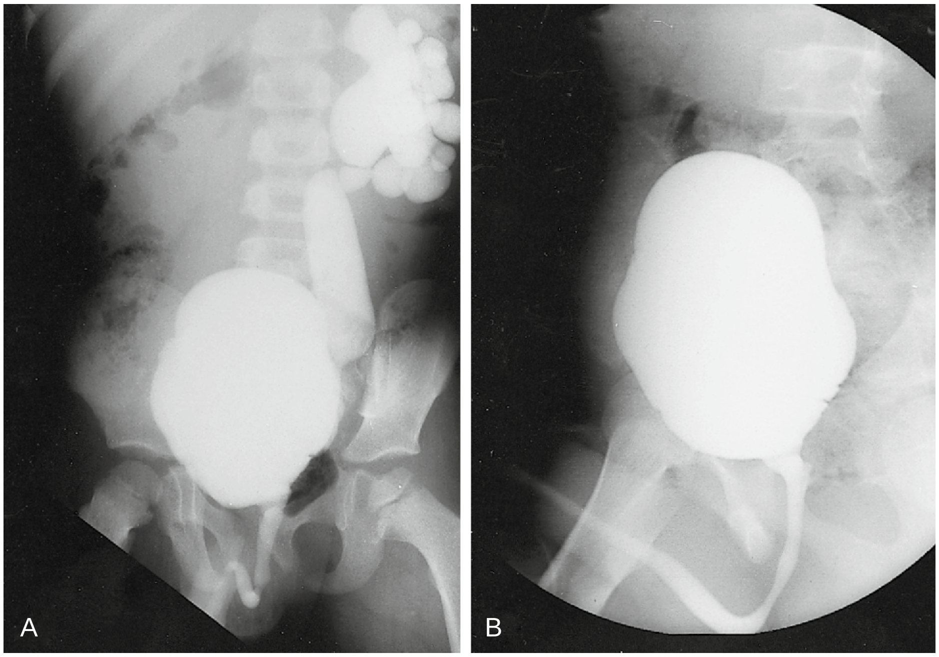

Figure 24-4 **A,** Voiding cystourethrogram shows high-grade left vesicoureteral reflux after failed reimplantation. **B,** Voiding cystourethrogram 1 year after endoscopic subureteral injection shows an absence of reflux in the same child.

treated with the STING procedure as outpatients. Using PTFE injections, successful resolution of VUR has been achieved in 90% of cases after multiple injections.[49,63,111] Reflux has resolved in 55% to 73% after a single PTFE injection.[49,61,63,111] Recurrence has been 30% in some series; however, this is often seen as an early phenomenon in the first 3 months after STING. More recently, Capozza and associates[140] reported on 50 patients in whom endoscopic therapy with Deflux failed, and 27 were considered to have dysfunctional voiding patterns. They concluded that uncontrolled voiding dysfunction contributed to endoscopic treatment failure. A study from Atlanta had a 78% success rate using Deflux to treat VUR in neurogenic bladders.[34] The investigators concluded that although open ureteral reimplantation was more effective than endoscopic therapy in treatment of VUR in children with bladder dysfunction, the simplicity of the technique of endoscopic correction makes it an excellent first-line therapy.

Reflux Secondary to Posterior Urethral Valves

VUR is present in almost 75% of children with posterior urethral valves.[141-143] Reimplantation of ureters for high-grade reflux secondary to posterior urethral valves is associated with a high complication rate.[143,144] Atwell[143] showed that 50% of children undergoing reimplantation of the ureter for high-grade VUR secondary to posterior urethral valves required further surgery for poor drainage from the upper tracts.

In a series of 54 children with posterior urethral valves at our institution, 38 (70%) had VUR, and 9 of these cases resolved after valve ablation.[145] Seven underwent nephroureterectomy for nonfunctioning kidneys, and two were treated with continuous chemoprophylaxis. The remaining 20 underwent an antireflux procedure: reimplantation in 5 and STING in 15. Of the 15 undergoing STING, 9 had bilateral reflux, and 6 had unilateral reflux. Reflux was grade IV in 6 and grade V in 18 ureters. Reflux was eliminated after a single injection in 17 ureters, 5 required two injections, and the remaining 2 ureters required three injections. Over a follow-up of 1 to 10 years, there has not been any recurrence of reflux. These results show that STING is a safe alternative to ureteral reimplantation for the management of high-grade VUR secondary to posterior urethral valves.

Endoscopic Treatment in Failed Reimplanted Ureters

VUR after reimplantation of ureters has been reported in 19% of cases.[11,146,147] Reoperation in failed reimplanted ureters is a major undertaking associated with significant morbidity.[148] STING has been found to be an effective procedure for the correction of VUR after failure of reimplantation of ureters.[57,78]

Between 1985 and 1995, 31 children with persistent high-grade VUR after failure of reimplantation of ureters were referred to our institution for endoscopic correction of reflux.[57] There were 18 boys and 13 girls 2 to 14 years old. Of children, 22 had unilateral reflux, and 9 had bilateral reflux, making a total of 40 refluxing ureters; 38 of the 40 ureters had grade III to V reflux. The underlying abnormality for reimplantation in the 40 ureters was primary VUR (n = 22), VUR in duplex systems (n = 4), VUR secondary to neuropathic bladder (n = 4), posterior urethral valves (n = 2), ureterocele (n = 2), bladder exstrophy (n = 4), and vesicoureteral junction obstruction (n = 2). The procedure for initial reimplantation of ureters in the 31 patients included the Cohen procedure (n = 15), the Politano-Leadbetter procedure (n = 12), the Glenn procedure (n = 3), and the Gilvernet procedure (n = 1). VUR was observed in all patients with chemoprophylaxis for at least 12 months before being referred to our unit.

After single subureteral PTFE injection, 27 ureters stopped refluxing; 7 refluxing ureters required two injections and 4 ureters required three injections for the correction of VUR. Failure to correct reflux by STING was noted in two ureters in a patient with bladder exstrophy. The results were uniformly good in all the types of reimplantation. At follow-up (1 to 11 years), no patient had recurrence of VUR (Fig. 24-4).

A study from Atlanta had an 88% success rate in treating 17 ureters after failed open reimplantation for VUR.[34]

A meta-analysis on endoscopic therapy for VUR found that endoscopic treatment after a previously failed open reimplantation was successful in 65% of cases.[129]

Endoscopic Treatment in Retained Ureteral Stumps

In children undergoing heminephrectomy for nonfunctioning upper pole moieties in duplex kidneys, a retained ureteral stump sometimes can be the cause of significant problems. There have been previous reports of successful management of these refluxing stumps using the STING procedure.[149] A more recent study has shown a 67% success rate after endoscopic treatment in refluxing ureteral stumps in six cases.[34] In the two failed cases, the ureteral orifice exited at the bladder neck. Endoscopic treatment in retained refluxing ureteral stumps should definitely be considered.

Neocontralateral Reflux after Antireflux Procedures

Contralateral VUR after unilateral open ureteral reimplantation has been reported in 10% to 32% of patients.[150-155] It has been suggested that surgical distortion of the contralateral trigone during the procedure[156] or the elimination of a low-pressure pop-off mechanism from the bladder[154] may result in contralateral neoreflux. In a series of 495 children undergoing a unilateral STING procedure for grades III to V reflux during 1985 to 1995, only 37 patients (7%) were found to have neocontralateral VUR after previous successful correction of VUR, with 40% of these occurring within the first 3 months. If this phenomenon of contralateral VUR was due to a pop-off mechanism, the incidence would be similar in open surgical and STING techniques; however, the low incidence with STING suggests that trigonal distortion during open surgery is the likely mechanism.[157]

Few studies have reported the incidence of new contralateral reflux after endoscopic correction of unilateral reflux.[21,128,158,159] Some authors have suggested that the contralateral ureter should be treated prophylactically in certain groups of patients undergoing unilateral endoscopic correction of VUR.[158] Our own series had a 10% incidence of new contralateral reflux and did not support prophylactic endoscopic treatment of the contralateral ureter in patients undergoing unilateral endoscopic correction of VUR.[159] In our series of 662 patients undergoing unilateral endoscopic correction of VUR, new contralateral VUR was diagnosed in 67 (10.1%) patients at follow-up voiding cystourethrogram. Half of these had low-grade new contralateral VUR and required no further treatment, and the other half with high-grade new contralateral VUR underwent successful endoscopic correction of VUR. There was no particular risk factor identified with the development of new contralateral VUR.

CONCLUSION

Endoscopic subureteral injection of tissue-augmenting substances has become an established alternative to long-term antibiotic prophylaxis and surgical intervention in the management of VUR in children. It is a simple 15-minute outpatient procedure. In terms of effectiveness and safety, Dx/HA is the most reliable and widely used injectable product for the endoscopic treatment of VUR.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 25

SURGERY FOR VESICOURETERAL REFLUX

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In the anatomically normal ureterovesical junction, the urine effluxes from the ureter into the bladder, but does not reflux back. Nature has accomplished this remarkable piece of bioengineering by resorting to the hydraulic principles of a *flap-valve* mechanism. The ureter travels obliquely within the bladder wall, and this unique configuration allows the increasing hydraulic pressure during bladder filling and emptying to compress the intramural portion of the ureter and prevent reflux. In patients with vesicoureteral reflux (VUR), the ureter enters the bladder at a right angle with respect to the bladder wall, resulting in a minimal intramural course. In addition, structural anomalies, such as a paraureteral diverticulum or ureterocele, weaken the back wall of the intramural ureter and can compromise the flap-valve mechanism further. Underlying lower urinary tract abnormalities, such as outlet obstruction (e.g., posterior urethral valves), neuropathic bladder dysfunction, and bladder instability, can also lead to an abnormal increase in intravesical pressures and contribute to reflux.

The goal of antireflux surgery is to restore the flap-valve mechanism of the ureterovesical junction by establishing an adequate submucosal tunnel of the intramural ureter. A general principle established by the experimental works of Paquin[1] states that the tunnel length must be at least five times that of the ureteral width. It is crucial, however, to ensure the normal functionality of the entire lower urinary tract as one considers the surgical reconstruction of the ureterovesical junction. To ensure a successful outcome after antireflux surgery, one must use meticulous surgical techniques, such as preserving ureteral vascularity, establishing a smooth course of the ureter through the ureterovesical hiatus, and providing a secure back wall support behind the submucosal tunnel against which ureteral compression can occur. The open surgical repair of VUR remains the “gold standard” against which other interventions are measured. It has a long track record of success, with most series reporting reflux correction in 95% to 98% of patients.

INDICATIONS FOR SURGICAL REPAIR

The treatment of VUR must be individualized. Several factors must be considered before deciding on surgery, including (1) the severity of reflux grade; (2) the age at presentation and the duration of reflux; (3) the presence and the quality of urinary tract infections; and (4) the possible underlying risk factors, such as bladder dysfunction and outlet obstruction. In most patients with mild to moderate degrees (grades I to III) of VUR, spontaneous resolution is likely to occur with time. The primary goal of medical management is to provide an infection-free period using prophylactic antibiotics during which spontaneous reflux resolution can occur without damaging renal parenchyma. There is an ongoing debate about whether reflux can cause renal damage in the absence of urinary tract infection, but at present there is no direct evidence to support this postulate.

The *absolute* indication for surgical correction of VUR is the failure of medical management, specifically breakthrough febrile urinary tract infections. Other *relative* indications include the presence of massive reflux (grade IV or V) with a low likelihood of spontaneous resolution; reflux associated with other anatomic problems, such as large paraureteral diverticulum; and impaired renal growth or function evidenced by ultrasonography or renal scan. Surgery also may be indicated in girls whose reflux persists after they have reached their full somatic growth potential at puberty, with the goal of preventing future problems, such as pregnancy-related complications and hypertension. This notion has been challenged, however, with proposals that if older patients have a mild to moderate degree of reflux without pyelonephritic renal scarring, they may require no further medical or surgical treatment *regardless* of the reflux status.[2] Additional studies are required to test the validity of this hypothesis further. Finally, the expectations for the outcome of surgery must be clearly understood by the patients and their families. Successful ureteral reimplantation significantly reduces the risk of pyelonephritis, but does not affect the incidence of lower urinary tract infections. Bacteriuria has been reported in 40% of patients after successful surgery, although most do not develop pyelonephritis.[3]

TECHNIQUES

Cystoscopy and Positioning

Cystoscopy may be performed under the same anesthetic at the time of the ureteral reimplantation (ureteroneocystostomy). Endoscopic evaluation of the entire lower urinary tract is advised, especially in patients whose preoperative voiding cystourethrography suggests an unusual anatomic situation. Cystoscopic evaluation can also reveal unexpected findings that were not appreciated on preoperative imaging studies. A duplex system with a distally located upper pole ureteric orifice may be discovered during cystoscopy. The upper pole ureter opening ectopically at the bladder neck or proximal urethra may be difficult to identify and easily missed from the intravesical exposure. If duplex ureters are widely separated from each other at the level of the trigone and bladder neck, the extravesical common sheath reimplantation approach may be unsuitable. In boys, the posterior urethra should be examined carefully for any evidence of outlet obstruction, such as posterior urethral valves. The presence of wall thickening and trabeculation should alert the clinician of a potential voiding dysfunction and outlet obstruction. If the bladder mucosa is inflamed diffusely, one must suspect a possible urinary tract infection, which may increase the likelihood of postoperative complications.

The patient is positioned supine with a slight break in the table to raise the hips, especially in obese children. Generally, the legs are gently spread open, and the perineum is prepared within the operative field. For extravesical ureteral reimplant, a Foley balloon catheter is inserted into the bladder to control the filling and emptying during the procedure.

Intravesical Approach

Exposure

A transverse suprapubic skin incision (Pfannenstiel) is made along a skin crease approximately one finger-breadth above the pubic symphysis. This incision provides an excellent

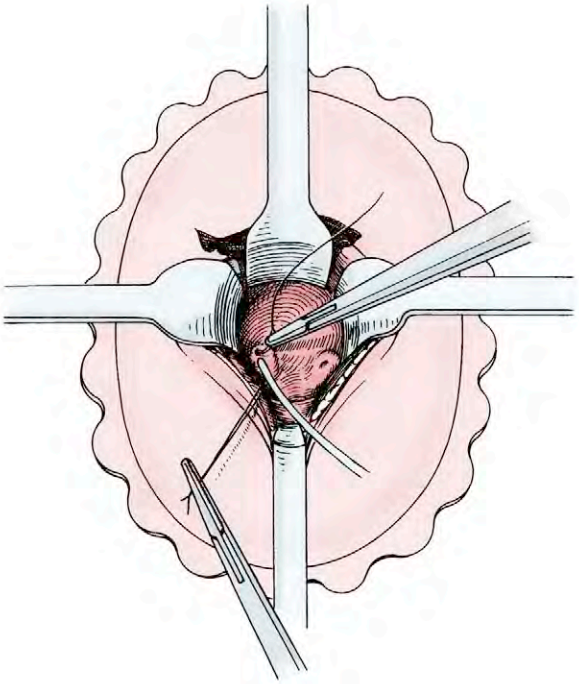

Figure 25-1 Denis Browne self-retaining retractors are positioned to flatten and elevate the posterior bladder wall, bringing the trigone and ureteric orifices into the middle of the operative incision. Fine chromic sutures are placed above and below the ureteric orifices for traction handles, and a small soft feeding tube is placed as an aid during the initial dissection of the ureter. (From Retik AB, Colodny AH, Bauer SB. Pediatric urology. In: Paulson DF, ed. *Genitourinary Surgery*. Vol 2. New York: Churchill Livingstone; 1984.)

exposure for routine ureteral reimplantations and yields a minimal scar that can easily be hidden by clothing. The anterior rectus sheath is opened either horizontally or vertically, and the rectus and pyramidalis muscles are split in the middle to expose the anterior bladder wall. A midline cystotomy is made in a vertical direction, extending inferiorly to within 1 cm of the bladder neck and superiorly to the dome, leaving a shelf of the bladder wall onto which a cephalad retractor can be hooked.

The Denis Browne universal retractor affords an ideal exposure for ureteral reimplantation (Fig. 25-1). It is important to protect the bladder neck from inadvertent tearing by securely suturing the inferior apex of the cystotomy incision to the rectus fascia. Moist sponges are packed gently into the dome of the bladder behind the cephalad retractor to stretch the posterior bladder wall taut. The overall goal of retractor positioning is to *elevate* and *flatten* the posterior bladder wall, bringing the trigone and the ureteric orifices into the middle of the operative field and close to the skin surface. Excessive manipulation of bladder mucosa with sponges, suction devices, or forceps should be avoided to prevent edema and inflammation, which may contribute to postoperative bleeding and bladder spasm.

Ureteral Dissection

A refluxing ureter often has a patulous orifice, is positioned lateral in the trigone, and has a straight course through the bladder wall. The interureteric ridge is usually poorly developed. The ureter is first intubated with a small, soft feeding tube (3.5F to 5F). Having a catheter in the ureter helps with the initial dissection, especially of the intramural portion. Fine (4-0) chromic sutures are placed immediately above and below the orifice as traction handles (see Fig. 25-1). Gentle traction on these sutures during dissection obviates traumatic handling of the ureters with forceps. The ureteric orifice is circumscribed sharply, leaving a 2- to 3-mm cuff of bladder mucosa. A needle tip cautery may be used instead of a knife or scissors during ureteral dissection to aid hemostasis, but must be used judiciously to preserve the periureteral vasculature. When the bladder mucosa surrounding the orifice has been incised, the medial bladder muscle that constitutes the lateral extension of the trigone is divided sharply toward the ureter until the ureteral wall is visualized within the Waldeyer sheath. Gentle spreading of this space with the curve of the scissors paralleling the course of the ureter establishes the subsequent plane of dissection (Fig. 25-2). Dissecting too close to the ureter risks damaging its adventitial blood supply, whereas dissecting too far away from the ureter can cause excessive bleeding. Kinks and angulations should be straightened carefully. Before dividing the periureteral tissues, one must clearly visualize the ureter and apply cauterization well away from the ureter. The ureter is dissected until 6 to 8 cm has been freed up. A gentle pull should provide a feel of a light "spring" coiling back without any tethering.

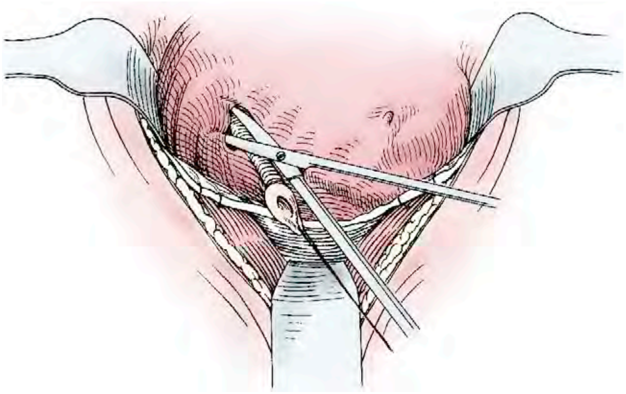

Figure 25-2 Tenotomy scissors are used to establish the correct plane of dissection inferiorly, which is carried around the circumference of the ureter. (From Retik AB, Colodny AH, Bauer SB. Pediatric urology. In: Paulson DF, ed. *Genitourinary Surgery*. Vol 2. New York: Churchill Livingstone; 1984.)

Politano-Leadbetter Technique

First described in 1958, the Politano-Leadbetter technique[4] has been widely used with excellent results. In this technique, the ureter is brought into the bladder through a new hiatus superior to the original hiatus. The ureter is placed in a submucosal tunnel directed toward the bladder neck. Success rates of 97% to 99% have been cited,[5] although some authors have reported a slightly higher complication rate compared with the relatively simple cross-trigonal method.[6] Most reimplants done currently are in the Cohen fashion because it is easier to perform and has fewer complications.

Cohen Cross-Trigonal Technique

First described by Cohen in 1975,[7] the versatile cross-trigonal reimplantation is probably the most popular technique used today. Achieving an adequate submucosal tunnel length along the posterior bladder wall is possible in virtually every patient. Cross-trigonal reimplantation is also the procedure of choice to move the ureteric orifices superiorly when bladder neck reconstruction is performed at the same time. The technique's one

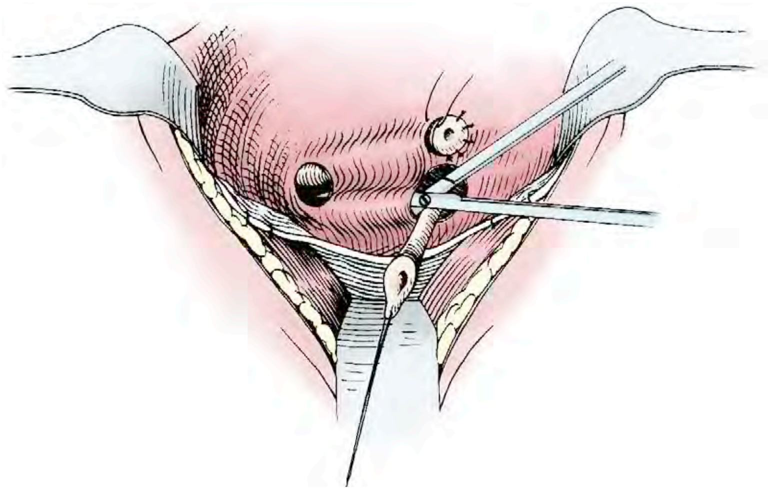

Figure 25-3 Bilateral Cohen cross-trigonal ureteral reimplantation. The ureters are dissected and mobilized as described in the text. The more superior ureter (typically with more severe reflux) is tunneled transversely to the new orifice just above the contralateral ureter. The inferior ureter is tunneled below the contralateral ureteral hiatus. (From Retik AB, Colodny AH, Bauer SB. Pediatric urology. In: Paulson DF, ed. *Genitourinary Surgery*. Vol 2. New York: Churchill Livingstone; 1984.)

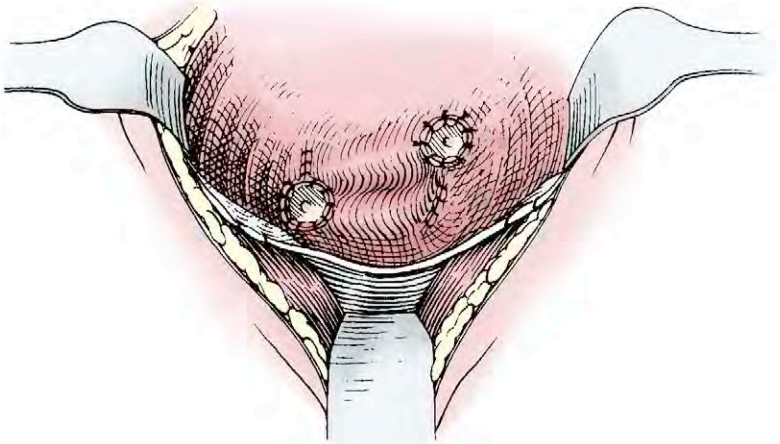

Figure 25-4 Appearance of the completed bilateral Cohen cross-trigonal ureteral reimplantation. (From Retik AB, Colodny AH, Bauer SB. Pediatric urology. In: Paulson DF, ed. *Genitourinary Surgery*. Vol 2. New York: Churchill Livingstone; 1984.)

potential problem is difficulty in retrograde catheterization or ureteroscopy or both because of the lateral deviation of the ureters away from the bladder neck. Technical advancements in flexible endoscopy may minimize this concern.

When the ureter has been mobilized, the original hiatus is inspected to see whether it requires narrowing. A large, patulous opening at the hiatus can lead to a diverticulum formation and should be reinforced, but during this maneuver one must be careful not to make it too tight because this would lead to postoperative obstruction. It is better to err on the side of leaving it slightly loose rather than too tight because a small diverticulum at the hiatus of the submucosal tunnel rarely causes clinical problems. If both ureters are being reimplanted, it is preferable to reimplant the more severely refluxing ureter above the ureter with less reflux because the upper ureter generally would have a slightly longer tunnel. To achieve longer tunnel lengths, the original hiatus can also be incised superiorly and laterally, using a broader area of the posterior bladder wall.

Bladder mucosa surrounding the ureteral hiatus is first undermined for a few millimeters using sharp tenotomy scissor dissection; this establishes the plan of dissection for the submucosal tunneling maneuver (Fig. 25-3). Bladder mucosa should be grasped firmly but gently, paying close attention not to tear it. One must be careful that the bladder muscle behind the tunnel is not too thin because this would lead to an ineffective flap-valve mechanism. If the bladder wall is very thin (as in infants), or if the bladder mucosa is too inflamed to identify the proper plane of dissection easily during the tunneling maneuver, it is better to incise the mucosa open, undermine it for few millimeters, and reinforce the back wall of the bladder muscle with several interrupted sutures. The ureter is laid down in this trough, and the mucosa is sutured over the ureter. The tunnel should be sufficiently wide so that the ureter is not constricted. The ureter is positioned through the tunnel without kinking or twisting. It is important to check the smooth course of the ureter by gently passing a small, soft feeding tube and watching for urinary efflux.

The anastomosis is performed using fine absorbable sutures (4-0 and 5-0 chromic catgut), approximating the bladder mucosa cuff surrounding the ureteric orifice to the new mucosal opening (Fig. 25-4). The advancing edge is sutured

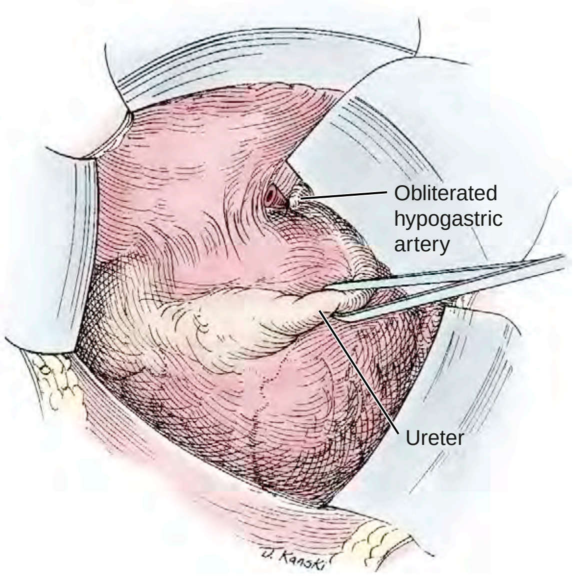

Figure 25-5 Exposure of the distal ureter in preparation for an extravesical antireflux procedure. The bladder has been emptied and rolled to the opposite side to expose the ureter. The ureter is easily found by dividing the obliterated umbilical artery and following it toward the iliac vessels. (From Peters CA, Retik AB. Ureteral reimplantation including megaureter repair. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: WB Saunders; 1996.)

to the bladder muscle to ensure that the ureter is securely anchored. The rest of the bladder mucosal defect is closed with fine absorbable sutures.

Closure and Postoperative Drainage

The cystotomy is closed in two layers using running absorbable sutures (such as 3-0 chromic or polyglycolic acid) after intravesical reimplants. Postoperative bladder drainage is typically accomplished through a small urethral catheter, but in young boys in whom the penile urethral caliber is too small to afford an adequate-size catheter, some surgeons prefer a suprapubic tube. In uncomplicated situations, ureters are not typically stented. With a secure two-layer cystotomy closure, urinary leakage is extremely rare, and in the authors' experience, the perivesical drain has been unnecessary in most cases.

Extravesical Approach

There has been a renewed interest in the use of the extravesical technique. In the contemporary reports, the results in terms of reflux correction seem comparable with the results of traditional intravesical techniques.[7-9] The main advantage lies in the fact that patients who undergo extravesical reimplantation experience significantly less postoperative hematuria and bladder spasm. Some authors have reported an excellent outcome in performing extravesical ureteral reimplantation in an outpatient setting or with a short overnight hospital stay.

In the extravesical technique, the submucosal tunnel required for the flap-valve mechanism is created outside the bladder lumen without detaching the ureter from the original ureterovesical junction. Bilateral extravesical repair should be done with caution, however, because urinary retention can result, presumably owing to denervation of the subtrigonal nerve plexus during ureteral dissection and tunnel development.[10] Retention rates after bilateral extravesical ureteral reimplants have ranged from 3% to 30%. In our experience, the incidence of urinary retention has been low, and the retention has all been transient, with normal voiding returning after several days of indwelling urinary catheter use. The urinary retention may be more common in young toddlers and in patients with preexisting voiding dysfunction.

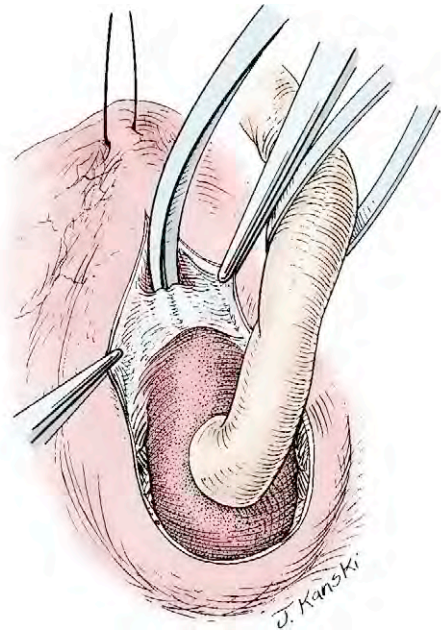

Figure 25-6 The ureter is completely mobilized down to the ureterovesical junction, and the bladder muscle fibers are divided to develop a muscular trough, exposing the back wall of the bladder mucosa. Having the bladder moderately full causes the mucosa to bulge outward and helps in dissection. The direction of the submucosal tunnel must be chosen carefully, taking into account the fact the bladder has been rolled to one side, so that the ureter does not angulate and kink. (From Peters CA, Retik AB. Ureteral reimplantation including megaureter repair. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: WB Saunders; 1996.)

Exposure

A Foley catheter is inserted into the bladder to control the bladder distention. When the prevesical space is exposed, the bladder is rolled to the side to expose the ureter. This maneuver is easier with the bladder empty. The ureter is identified and dissected from surrounding structures toward the ureterovesical junction. The most reliable way to find the ureter is first to identify the obliterated umbilical artery and follow it posteriorly toward the iliac vessels (Fig. 25-5). The ureter is typically found crossing just below the obliterated umbilical artery between the bladder and the peritoneum. Dividing the obliterated umbilical artery also facilitates sweeping the peritoneum superiorly and improves the overall exposure.

There are many small vessels converging near the ureterovesical junction, and they need to be carefully ligated, cauterized, and divided. After the ureter has been completely mobilized, the bladder muscle fibers are incised superior to the ureterovesical junction to develop a submucosal tunnel (Fig. 25-6). As the muscle fibers are divided, the backside of the bladder mucosa becomes visible. Having the bladder moderately full at this point causes the bladder mucosa to bulge outward, making dissections easier. This trough should be long enough to provide an adequate width-to-length ratio

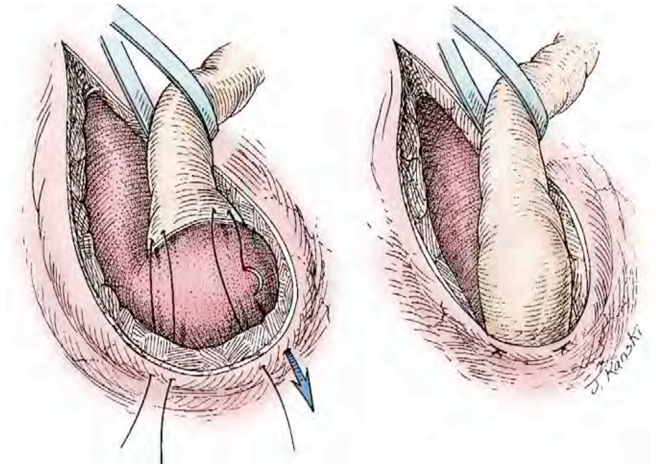

Figure 25-7 Fine absorbable sutures are placed as paired horizontal mattress sutures to advance the ureter underneath the shelf of bladder muscle toward the bladder neck. This maneuver effectively anchors the ureter within the submucosal tunnel and prevents "dessusception" of the ureter. (From Peters CA, Retik AB. Ureteral reimplantation including megaureter repair. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: WB Saunders; 1996.)

in correcting the reflux. The direction of the tunnel must be carefully chosen, taking into account the fact that the bladder has been rolled to one side to expose the ureterovesical junction. When the retractor is released, the bladder is returned to the normal position, and the ureter must course smoothly through the new hiatus without angulation.

The backside of the bladder mucosa is exposed continuously down to the ureterovesical junction, and the dissection is continued distal to the ureterovesical junction for approximately 1 to 2 cm. The ureterovesical junction should be freely mobile so that it can be dropped into the bladder lumen during the imbrication of muscle layers over the ureter. The ureter is advanced toward the bladder neck by incorporating the ureterovesical junction to the bladder muscle at the inferior apex of the tunnel (Fig. 25-7). This is an important step, which prevents slippage or "dessusception" of the ureter. Two 5-0 polyglycolic acid sutures are placed to advance the ureter underneath the shelf of the bladder muscle. The muscle layers are approximated over the ureter using 4-0 polyglycolic acid sutures to form the submucosal tunnel (Fig. 25-8). The new hiatus should be loose, accommodating a blunt right-angle clamp beside the ureter at the proximal end of the tunnel. The bladder is allowed to roll back into its natural position, and the course of the ureter is checked to ensure that it is not angulated.

POSTOPERATIVE MANAGEMENT

Careful attention should be paid to ensure that a brisk diuresis is maintained postoperatively. Until the oral intake of fluid is adequate, a generous amount of intravenous fluid should be administered. Diet is advanced quickly, with most patients resuming a regular diet by the next day. In our experience, the most troublesome postoperative issue after intravesical ureteral reimplantation has been bladder spasm. The pain from the operative incision becomes minimal in most patients after 1 to 2 days, but the bladder spasms can persist for several days. Many agents, such as opioids, local anesthetics, anticholinergics, and antispasmodics, have been tried with modest efficacy.

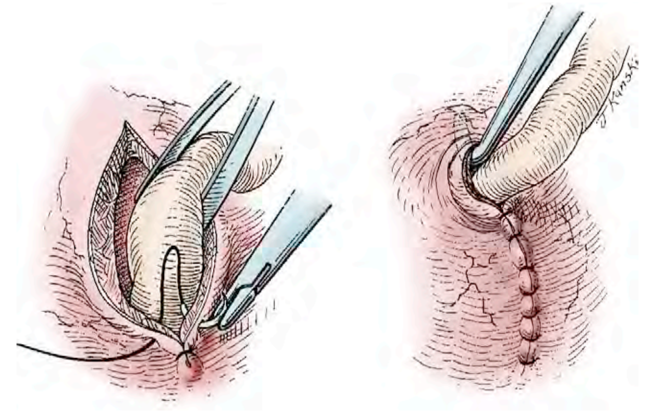

Figure 25-8 The muscular trough is closed over the ureter using interrupted absorbable sutures. The new hiatus must be confirmed to be loose to prevent obstruction. (From Peters CA, Retik AB. Ureteral reimplantation including megaureter repair. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: WB Saunders; 1996.)

One of the most effective agents in our recent experience has been parenterally administered ketorolac tromethamine. It is an injectable form of nonsteroidal anti-inflammatory drug; such drugs reduce the tissue prostaglandin levels by inhibiting cyclooxygenase. In a double-blind randomized trial, patients who received ketorolac intravenously experienced significantly fewer and less severe bladder spasms than patients who received placebo. Ketorolac therapy should be started early, typically at the conclusion of the surgery (0.5 mg/kg per dose intravenously, maximum of 15 mg per dose) and maintained every 6 hours for 48 to 72 hours. Using ketorolac longer than 5 days has been associated with a higher incidence of adverse effects, such as renal dysfunction and gastrointestinal bleeding. Because of these concerns, some have recommended limiting the number of doses to three to six postoperatively in children. Patients must be well hydrated while they receive ketorolac because hypovolemia can increase the risk of renal dysfunction. Ketorolac should not be given to infants younger than 1 year because prostaglandin production is thought to play an important role during renal maturation.

The bladder catheter is typically removed after 2 to 3 days for intravesical reimplantation and sooner for extravesical surgery. Patients are followed within 4 to 6 weeks with an upper tract imaging study (e.g., renal ultrasonography) to rule out an obstruction. A mild degree of ureteral dilation can be seen occasionally at this time, especially if the reimplantation was performed for high-grade reflux. Radionuclide or contrast voiding cystourethrography is performed 3 to 4 months postoperatively to document that the reflux has been corrected. Because of the high rate of success, some authors have advocated eliminating postoperative voiding cystourethrography in patients undergoing open surgical repair for mild to moderate reflux. Patients should be carefully instructed to continue prophylactic antibiotic therapy until postoperative evaluations are completed.

SPECIAL CONSIDERATIONS

Duplex Ureters (Common Sheath Reimplantation)

Often VUR is associated with the lower pole ureter of a duplex collecting system. As predicted by the Weigert-Meyer rule of ureteral embryology, the lower pole ureter enters the bladder in a more lateral and superior location relative to the trigone and the bladder neck, and it results in a shorter intramural ureter. Although the upper pole ureter does not usually reflux, it should be dissected and reimplanted as one unit along with the lower pole ureter in a common sheath of Waldeyer. Near the ureterovesical junction, two ureters are adjoined tightly in a common sheath, sharing a common adventitial blood supply, and separating the lower ureter from the upper one at this location is likely to lead to devascularization injury to both.

When the upper pole ureter drains ectopically into the bladder neck, urethra, or other wolffian duct structures, it is difficult to perform the common sheath reimplantation using the same mucosal cuff. In this situation, the upper pole ureter is best dissected separately through a trigonal incision distal to the lower pole orifice. It is divided from the distal portion inserting into the ectopic location. After the upper pole ureter is mobilized adequately, it is reimplanted alongside the lower pole ureter. In common sheath reimplantation, one must pay close attention to ensure that submucosal tunnels are of sufficient width and length to accommodate both ureters.

Paraureteral Diverticulum

In some instances, reflux is associated with a paraureteral diverticulum. The presence of a large diverticulum makes it unlikely that reflux would resolve spontaneously with time. The diverticulum is dissected together with the ureter, and the muscular defect is carefully reinforced to provide a secure back wall of the submucosal tunnel.

MANAGEMENT OF COMPLICATIONS

Early Obstruction

Obstruction at the newly created ureteroneocystostomy site is the most common complication within the first 4 weeks after surgery. Rarely, this obstruction may be entirely silent, being discovered only by worsening hydronephrosis seen on imaging studies. More often, symptoms such as abdominal pain, anorexia, or emesis occur. Fever is unusual. The underlying cause is typically edema at the site of anastomosis, hematoma at the site of dissection, or kinking at the reimplantation site. Transient obstruction may occur secondary to mucus or blood clots plugging the ureter. In most cases of early obstruction, an observational approach is warranted, using supportive measures and serial ultrasound examinations. Rarely, drainage is indicated in patients with fever, azotemia, acidosis, or electrolyte imbalance. If drainage is required, percutaneous nephrostomy is preferable to retrograde stenting. Often, the obstruction resolves shortly after decompression.

Persistent Obstruction

Persistent obstruction can be entirely silent and lead to renal loss. The cause of such obstruction is typically ureteral ischemia or improper placement of the reimplanted ureters. Intermittent obstruction due to “J” hooking near the ureterovesical junction can be seen with bladder filling. Percutaneous dilation may be tried first, but is typically of limited value. Reoperative reimplantation is the definitive treatment. In this situation, one must be prepared for various reconstructive options. A preoperative antegrade or retrograde ureterogram helps to delineate the level of obstruction and define the appropriate surgical strategy.

A midline incision, rather than a low transverse suprapubic incision, is preferred when dealing with persistent obstruction in the event a superior dissection is necessary. The bladder is exposed and opened, and ureteral dissection is started intravesically similar to the routine reimplantation, but one must not hesitate to extend the ureteral mobilization superiorly by going outside the bladder. The ureter must be mobilized completely, by reflecting colon medially if necessary. When dissecting the ureter, all the periureteral tissues should be swept toward the ureter, including the gonadal vessels, to preserve the ureteral vascularity. The fibrotic ureter must be cut back until a viable ureteral segment is encountered with a good blood supply. If there is an ample ureteral mobility to reach the bladder without tension, one can proceed with ureteral reimplantation using previously described techniques. If the ureter does not reach the bladder easily, one should consider additional bladder mobilization and upward fixation using the psoas hitch technique. The bladder is tented superiorly toward the ureter, and the new ureterovesical hiatus is made.

The outer wall of the bladder is sutured deeply to the psoas muscle using either polydioxanone or polypropylene (Prolene). The ureter is brought into the bladder through the new hiatus and reimplanted with a long tunnel similar to the Politano-Leadbetter technique. If the ureter does not reach the bladder easily with the psoas hitch alone, one can consider performing a Boari flap procedure, in which a rectangular strip of bladder is raised with a broad base and tubularized to meet the ureter. One potential limitation using the Boari bladder flap technique is the difficulty in establishing an effective submucosal tunnel. An additional length can also be obtained by wide mobilization of the kidney from its bed and suturing the lower pole of the kidney to the psoas muscle inferiorly.

Another reconstructive strategy is transureteroureterostomy, in which the obstructed ureter is anastomosed to the normal contralateral ureter. The ureter to be drained is widely mobilized without devascularization and brought across to the other side without tension. It should not be wedged beneath the inferior mesenteric vessels. An end-to-side anastomosis is performed using fine chromic or other absorbable interrupted sutures, and the ureter is drained using a soft feeding tube, brought through the bladder wall. In situations in which the ureter is too short for any of the previously described reconstructive options, one can consider ureteral substitution using a small bowel segment or renal autotransplantation. If both ureters need to be reimplanted and are too dilated for a small bladder, it is better to perform a transureteroureterostomy and reimplant only one ureter, rather than reimplant both ureters with an inadequate submucosal tunnel.

Persistent Reflux

Persistent reflux after ureteral reimplantation is unusual, but can occur owing to inadequate tunnel length or ureterovesical fistula. Beyond the technical reasons, one must consider the possibility of unrecognized voiding dysfunction, outlet obstruction, or neuropathic bladder. Generally, a trial of observation is worthwhile using prophylactic antibiotics because postoperative reflux often resolves spontaneously within 1 to 2 years. Massive reflux with recurrent pyelonephritis is best managed with surgical repair, following operative principles similar to those outlined for persistent obstruction. Preoperative cystoscopy is crucial in assessing the cause of persistent reflux.

In contrast to the obstructive situation, reoperative reimplantation for persistent reflux can be performed satisfactorily through a low transverse suprapubic incision. Occasionally, persistent reflux is seen despite the adequate submucosal tunnel length-to-width ratio, and this can be remedied with reoperative creation of a "superlong" tunnel (≥10:1) or by transureteroureterostomy to the nonrefluxing ureter. New contralateral reflux can be seen in 10% to 15% of patients after unilateral ureteral reimplantation. This reflux resolves within 1 to 2 years in most cases with observation. The cause of contralateral reflux after ureteral reimplantation is unknown, but may be due to a missed reflux on a preoperative cystogram, alteration of trigonal anatomy, or unrecognized bladder dysfunction.

REFERENCES

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CHAPTER 26

URETERAL DUPLICATION, ECTOPY, AND URETEROCELES

Kenneth G. Nepple, Christopher S. Cooper, and Howard M. Snyder III

Children with congenital anomalies of the ureter frequently present to the pediatric urologist. These anomalies include duplications, ureteroceles, and ectopy, and present fascinating reminders of the intricacy of our embryology. A knowledge of normal embryology and the accepted terminology employed for ureteral anomalies facilitates discussion of these anomalies.

TERMINOLOGY

Owing to previous confusion over earlier terminology, a standard set of definitions used to describe ureteral duplication anomalies now exists. These definitions were established by the Urologic Section of the American Academy of Pediatrics Committee on Terminology, Nomenclature, and Classification.[1] A *duplex (duplicated) system* refers to a kidney with two pelvicalyceal systems generally referred to as the *upper* or *lower poles*. If the kidney has two ureters that empty separately into the bladder *(double ureters)*, it is considered a *complete duplication*. In contrast, in a *partial* or *incomplete duplication*, a common single ureter enters the bladder. A *bifid system* is a form of duplication with two pelvicalyceal systems joining at the ureteropelvic junction (bifid pelvis) or before emptying into the bladder (bifid ureters).

The *upper* or *lower pole ureter* describes the ureter draining the upper or lower pole of a duplex kidney. The orifice associated with the ureter draining the upper or lower pole is known as the *upper* or *lower pole orifice*. A *laterally ectopic* ureter inserts lateral to the normal position. A *medially* or *caudally ectopic ureter* inserts medial and distal to the normal position on the trigone. An *ectopic ureter* drains to an abnormal site and generally refers to an orifice located medially or caudally.

A *ureterocele* is defined as a cystic dilation of the intravesical submucosal ureter. Ureteroceles contained entirely within the bladder are classified as *intravesical ureteroceles*, whereas *ectopic (extravesical) ureteroceles* contain a portion permanently situated at the bladder neck or in the urethra. A *single-system ureterocele* is associated with a kidney with only one ureter. A *duplex-system ureterocele* is associated with the upper pole of a kidney with a complete ureteral duplication.

EMBRYOLOGY

The ureter forms from the ureteral bud, which arises as a diverticulum from a ventral bend or elbow in the mesonephric (wolffian) duct at the end of the 4th week of gestation. This bend occurs as the mesonephric duct comes off the posterior wall crossing the metanephros from lateral to medial to reach the cloaca.[2] The ureteral bud grows off the bend in the mesonephric duct and penetrates the metanephric blastemal ridge, the kidney progenitor, late in the 5th week (Fig. 26-1). The ureteral bud subsequently forms the ureter, renal pelvis, calyces, papillary ducts, and collecting tubules. The metanephros differentiates into the more proximal portions of the nephron. The process of branching of the ureteric bud is complete by about 14 weeks, but new nephrons are produced throughout gestation.

The *common excretory duct* consists of the inferior portion of the mesonephric duct between the origin of the ureteral bud and the cloaca. This segment along with a short segment above the ureteral bud expands and inverts into the posterior aspect of the urogenital sinus by the 8th week of development, forming one half of the trigone (Fig. 26-2). The exact mechanism resulting in the incorporation of the ureteral bud into the urogenital sinus, separate from the mesonephric ducts, remains unclear.[3] Initially, the location of the ureteral bud orifices in the urogenital sinus is below and medial to the mesonephric duct orifices and in close proximity. With development, the ureteral orifices migrate cephalad and laterally, whereas the mesonephric duct orifices move caudally and medially. By the 12th week of gestation, the mesonephric duct reaches its final entry position in the posterior urethra at the level of the verumontanum in the male. The mesonephric duct becomes part of the epididymis, seminal vesicle, and vas deferens in the male and becomes the Gartner duct in the female. This migration explains why the vas deferens crosses over the ureter ventrally.

Incomplete ureteral duplication results from a ureteral bud that bifurcates shortly after its origin from the mesonephric duct. If the division occurs after the ureteral bud penetrates into the metanephric blastema (5th week of gestation), a bifid pelvis results. If the division occurs before the 5th week of gestation, varying degrees of ureteral duplication result with fusion distally as a single ureter entering the bladder. A duplex kidney with complete double ureters requires two ureteral buds arising from the mesonephric duct (Fig. 26-3A).

A more laterally and cranially placed lower pole ureteral orifice is often associated with primary vesicoureteral reflux (VUR). This abnormal orifice location is the result of a ureteral bud originating at a lower than normal position on the mesonephric duct and arriving early at the urogenital sinus. The early incorporation of this ureteral bud into the urogenital sinus permits it to migrate more laterally and cranially than normal. In this position, weakened trigonal support for the ureter might be expected, permitting VUR.[4-6]

When a ureteral bud originates slightly higher than normal on the mesonephric duct, it is incorporated into the urogenital sinus later than normal. This results in a shorter cranial and lateral migration, producing a minor displacement of the ureteral orifice caudally and medially toward the bladder neck. When the ureteral bud originates significantly higher than normal on the mesonephric duct, it might fail to incorporate into the bladder altogether and end in the urethra or mesonephric remnants. In the male, this can result in an ectopic ureter to the epididymis, vas, or seminal vesicle. In the female, the Gartner duct is the distal remnant of the mesonephric duct that runs from the broad ligament of the uterus along the lateral wall of the vagina to end at the hymen. A very high origin of the ureteral bud in the female could end anywhere along this duct and, with secondary rupture of the duct into

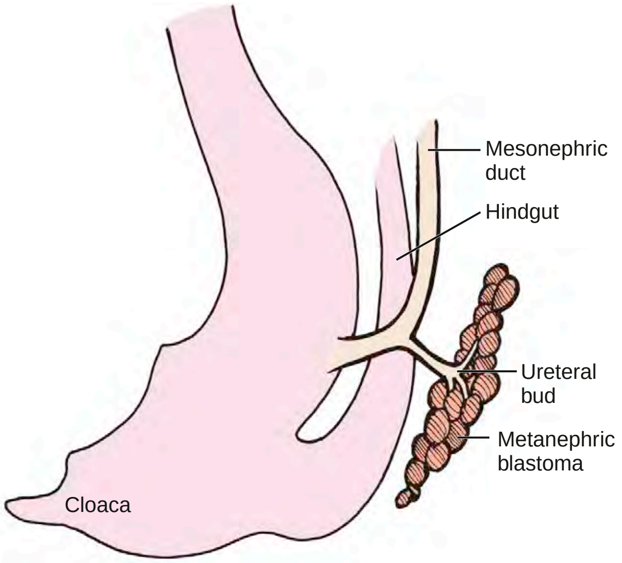


Figure 26-1 Normal embryology of ureteral bud from the mesonephric duct penetrates the metanephric blastemal ridge.

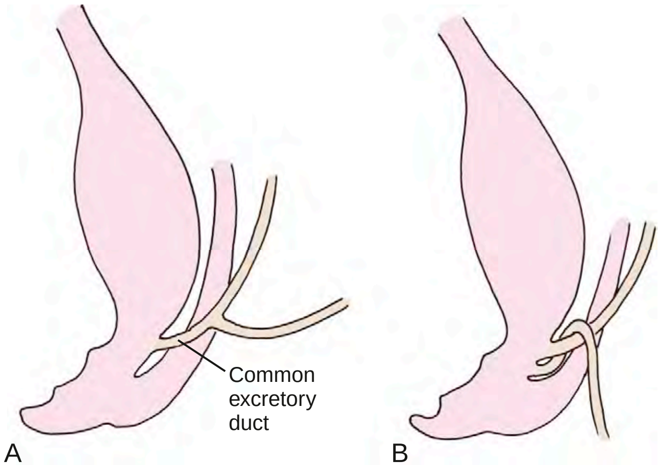


Figure 26-2 **A,** The ureteral bud expands and inverts into the urogenital sinus by the 8th week of development. **B,** The ureteral orifice migrates cephalad and laterally, while the mesonephric duct moves distally and medially.

the vagina, result in a vaginally ectopic ureter. In the male, an ectopic ureter always terminates above the level of the external urethral sphincter, so urinary incontinence is uncommon. In the female, by contrast, an ectopic ureter commonly exits below sphincteric control, creating constant wetting from the ectopic ureter and normal voiding of urine from other ureters terminating in the bladder.

When two ureteral buds originate with one located normally and one low, the result is complete duplication with VUR into the ureter, which during migration was carried most cranially and laterally, which is the lower pole ureter (Fig. 26-3B). This anomaly is a frequent clinical finding.[7] With a duplication of the ureteral bud with one in a normal location and one high, the high ureteral bud ends more caudally and medially than normal. The upper pole ureter is the one that ends ectopically (Fig. 26-3C). The Meyer-Weigert law states that when complete ureteral duplication exists, the medial and caudal ureteral orifice is that of the ureter to the upper pole of the kidney.[8,9]

The embryology of all ureteroceles cannot be explained by one model. In the embryo, Chwalla[10] described a two–cell layer ureteral membrane that is present at the time the ureteral bud arises from the mesonephric duct and later recedes. If this membrane does not completely break down, an obstructed ureteral-meatal orifice could result, leading to the formation of a ureterocele. The ureteroceles seen with stenotic orifices or associated with muscular hypertrophy of the ureteral wall support Chwalla's model. Stephens[2] and others have described cases, however, in which ureteroceles are found to have large patulous ureteral orifices that are difficult to explain with Chwalla's model. Alternatively, it has been suggested that the distal ureteral segment may be acted on by the same forces that cause the expansion of the urogenital sinus to form the bladder.[11-13] Tanagho's model[12,13] suggests that delay in establishment of the lumen of the ureteral bud with that of the mesonephric duct could result in ureteral expansion secondary to the same process that results in expansion of the urogenital sinus into the bladder. If this model were a complete explanation for ureterocele formation, all caudal ectopic ureters should be associated with a ureterocele, which is not the case.

Renal tissue associated with ectopic ureters and ureters joining ureteroceles is frequently dysplastic or hypoplastic. Mackie and Stephens[14] suggested that this finding could be associated with an abnormal origin of the ureteral bud from the mesonephric duct. According to this theory, the metanephric ridge is made up of blastema with variable potential for the formation of normal renal tissue. The best potential exists in the center of the ridge where it is normally penetrated by the ureteral bud. On either side of the center of the metanephric ridge, the blastema may have a decreased potential to form normal renal tissue. If the ureteral bud is located above or below the normal point of origin, it may grow to induce abnormal renal tissue from blastema with an increased propensity for dysplasia or hypoplasia. This theory seems to hold best for the upper pole ureters seen in complete duplications associated with ectopic ureters or ureteroceles, which are often associated with dysplastic or hypoplastic renal tissue. Less commonly, lateral ectopic lower pole ureteral orifices associated with VUR drain dysplastic or hypoplastic renal tissue.

URETERAL DUPLICATION

In an autopsy population, ureteral duplication occurs in 1 in 125 patients (0.8%) and constitutes the most frequent ureteral anomaly.[15,16] The right and left kidneys are affected equally. Bilateral duplication occurs in about 20% to 40% of cases.[17,18] There are twice as many girls as boys with duplications.[18] Urinary tract infection (UTI) is the most common associated finding, and the incidence of childhood UTIs is increased with duplications, as might be expected with the associated increased incidence of reflux or obstruction. A study of more than 700 children presenting with UTI found that 8% had ureteral duplication.[18] In one clinical series of patients with urinary symptoms, there was a much higher incidence of duplication: 2% to 4%.[19]

Duplication may be transmitted as an autosomal dominant trait with incomplete penetrance.[20] When an index child with a duplication is found in a family, the frequency of a sibling with a duplication increases from 1 in 25 to 1 in 8 or 9.[21-23] Other urinary tract anomalies associated with ureteral duplication include renal scarring or hydronephrosis or both.[24] In children who present with UTI and are found to have ureteral duplication, associated ectopic ureteroceles are present

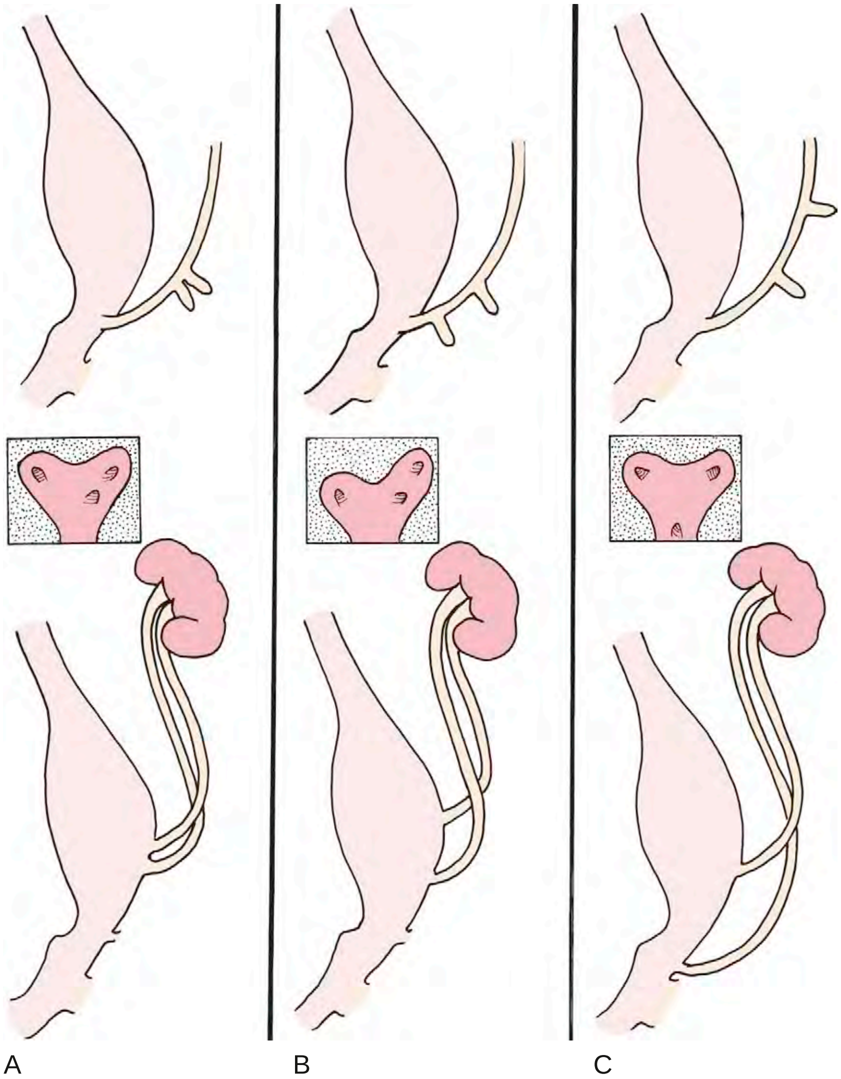


Figure 26-3 **A,** Complete ureteral duplication formed by two ureteral buds originating from a normal site on the mesonephric duct. The Weigert-Meyer rule stating that an upper pole orifice is medial and caudal to the lower pole orifice results from the rotation of the ureters during incorporation into the trigone. **B,** One of the two ureteral buds has a lower than normal origin, resulting in complete duplication with vesicoureteral reflux into this ureter, which during migration was carried most cranially and laterally. **C,** One of the two ureteral buds has a higher than normal origin, resulting in complete duplication with an ectopic upper pole ureter. (**A-C,** Redrawn from Snyder HM III. Anomalies of the ureter. In: Gillenwater JY, Howards SS, Grayhack JT, Duckett JW, eds. *Adult and Pediatric Urology*. 3rd ed. St. Louis: Mosby-Year Book; 1996.)

in 6% to 20% of children.[18,25] Histologically, renal hypoplasia or dysplasia and pyelonephritic scarring have an increased incidence.[16,26]

The presence of a ureteral duplication by itself is not an indication for intervention because many duplications may be incidentally noted. Consideration of a surgical procedure is indicated based on the presence of associated abnormalities (VUR, ureterocele, ectopic ureter, obstruction, or nonfunctional moiety); management is discussed in subsequent sections.

Incomplete Ureteral Duplication: Y Ureter

A ureteral bud that bifurcates early results in an incomplete duplication. A bifid renal pelvis is the result of the most proximal anatomic level of bifurcation and occurs in about 10% of the population. Of the other incomplete duplications, approximately 25% each are found to divide in the proximal or distal third of the ureter, and the remaining 50% divide in the middle section. Most partial duplications are discovered incidentally; however, with a Y junction in the ureter, it is possible for urine to be passed down to the junction and then, in a retrograde fashion, up the other side of the Y.[27,28] This "yo-yo" ureteral reflux is most common when the bifurcation is at a low position, but is rare if the duplication ends in the intramural portion of the ureter.[29] There may be associated urinary stasis, infection, ureteral dilation, or flank discomfort, but these findings are rare. Diagnosis is established by intravenous pyelogram (IVP) or fluoroscopy showing the ureteral reflux.[30] A voiding cystourethrogram (VCUG) is essential to eliminate ureteral dilation owing to VUR.

When surgery is necessary, and the duplication is very low, a conversion to complete duplication with reimplantation of the ureters into the bladder with separate ureteral orifices may be possible.[31] In cases with a higher duplication and single ureteral obstruction, a ureteropyelostomy or ureteroureterostomy at the kidney level with excision of most

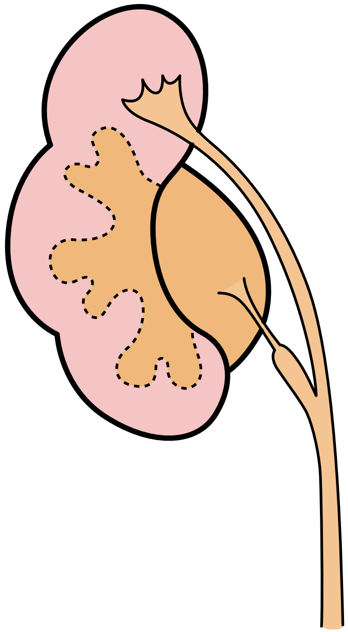


Figure 26-4 Ureteropelvic junction obstruction in the lower pole of the duplex kidney. Usually the lower pole ureter is too short for a ureteropyelostomy, and a side-to-side anastomosis of the pelvis to the upper pole ureter is performed. (From Gillenwater JY, Howards SS, Grayhack JT, Duckett JW. *Adult and Pediatric Urology*. 3rd ed. St. Louis: Mosby-Year Book; 1996:2204.)

of the distal obstructed ureter is curative.[32] Occasionally, ureteropelvic junction obstruction of the lower moiety may be found in association with incomplete duplex systems and poses interesting reconstructive problems.[33] Usually, the lower pole ureter is short, and a side-to-side anastomosis of the obstructed lower pole pelvis to the upper pole ureter is required (Fig. 26-4).

If a ureteral bud bifurcates, but only one limb induces the associated metanephric blastema, a rare form of incomplete duplication with one blind-ending ureteral branch is generated.[34-36] Most of these duplications are in the middle or distal right ureter and affect women three times more often than men. Occasionally, a long blind-ending ureter may end in the bladder and be confused with a periureteral diverticulum because of the frequent association of VUR.[37] The blind-ending ureter rarely causes symptoms, but it may generate flank pain associated with infection or calculi. A retrograde ureterogram may be required for diagnosis because the blind duplication may not fill on IVP. Treatment consists of surgical excision of the blind-ending ureter or entire duplication if clinically indicated.

When two separate ureteral buds arise from the mesonephric duct, but fuse before penetrating the metanephric ridge, an inverted Y ureter is generated. This very rare anomaly has been seen almost exclusively in girls.[38] If one limb is distally ectopic, urinary incontinence may result. Treatment is directed at problems caused by the ectopic limb; resection is usually required.

Complete Ureteral Duplication and Vesicoureteral Reflux

The combination of ureteral duplication and VUR is commonly seen in pediatric urology. VUR constitutes the most common cause of acquired renal disease in complete ureteral duplication. The presence of complete ureteral duplication seems to increase the likelihood that reflux will be found. A child with duplication and reflux presents most commonly with UTI. Fehrenbaker and coworkers[39] found reflux in 72% of children with duplex systems who presented with UTI. In another study by Siomou and colleagues,[18] children were evaluated for UTI, and reflux was present in 66% of complete duplications, 47% of incomplete duplications, and 26% of single systems. IVP and VCUG establish the diagnosis by showing a duplex renal system with VUR (Fig. 26-5). Isotope renal scintigraphy using technetium 99m dimercaptosuccinic acid (Tc^{99m}-DMSA) or technetium 99m mercaptoacetyltriglycerine (Tc^{99m}-MAG3) has proved to be an appropriate method to evaluate scarring and differentiate renal function between the upper pole and the lower pole.[40-42]

Reflux typically occurs into the lower moiety of a duplicated kidney drained by a ureter with a laterally ectopic ureteral orifice and shortened submucosal tunnel.[7] The upper pole ureter with its orifice medial and more caudal (Meyer-Weigert law) has a longer submucosal tunnel and usually does not reflux. When reflux into upper and lower pole ureters occurs, both orifices are usually side by side in a laterally ectopic position. Reflux into the upper pole ureter also may occur if its orifice is ectopic in the bladder neck or urethra because the ureter reaches this point separately without trigonal support for an adequate submucosal tunnel.

Traditionally, patients with duplex systems and reflux were treated more aggressively than a patient with a single system. It has now been shown by Afshar and associates[43] that when the grade of reflux is low (I or II), there is a substantial chance of resolution in duplex systems similar to resolution in single systems, although the resolution rate is slower (half resolved at 84 months versus 54 months). Linear growth of the child accompanied by lengthening of the submucosal tunnel of the ureter usually avoids the need for surgery.[43-45] Antibiotic prophylaxis and scheduled radiographic monitoring suffice for treatment, unless breakthrough urinary infection or new renal scars develop.

Since the description of endoscopic subureteral bulking agent implantation for correction of VUR in the 1980s,[46,47] endoscopic therapy has gained popularity because of its perception as a safe, minimally invasive, and effective procedure. A 2006 meta-analysis of different agents used in the endoscopic treatment of VUR found that patients with a duplicated system had a significantly lower success rate of 50% compared with patients with a single system (73%).[48] The lower success rate may be secondary to malposition or movement of the injected agent secondary to altered ureteral anatomy.[48,49]

Open surgical management is more appropriate in high-grade reflux because the likelihood of spontaneous resolution is small. Afshar and associates[43] reported that in duplex systems only 7% of grade III and no grade IV or V reflux resolved. In a complete duplication, the distal 2 to 3 cm of the two ureters usually are bound in a common muscular sheath, making their separation dangerous to one or both ureters because of the risk of devascularization. Surgical correction involves mobilization and reimplantation of the common sheath even though reflux has been observed in only one ureter.[50,51] The success rate of greater than 95% with common sheath ureteral reimplantation in duplicated systems is similar to that of single-system reimplantation.[52] When the lower pole parenchyma is very diminutive, a common sheath reimplant generally still suffices, unless there is major ureteral dilation that requires ureteral plication or tailoring or a ureteroureterostomy. Rarely, partial nephrectomy of a nonfunctioning segment is undertaken, and the fate of the refluxing distal

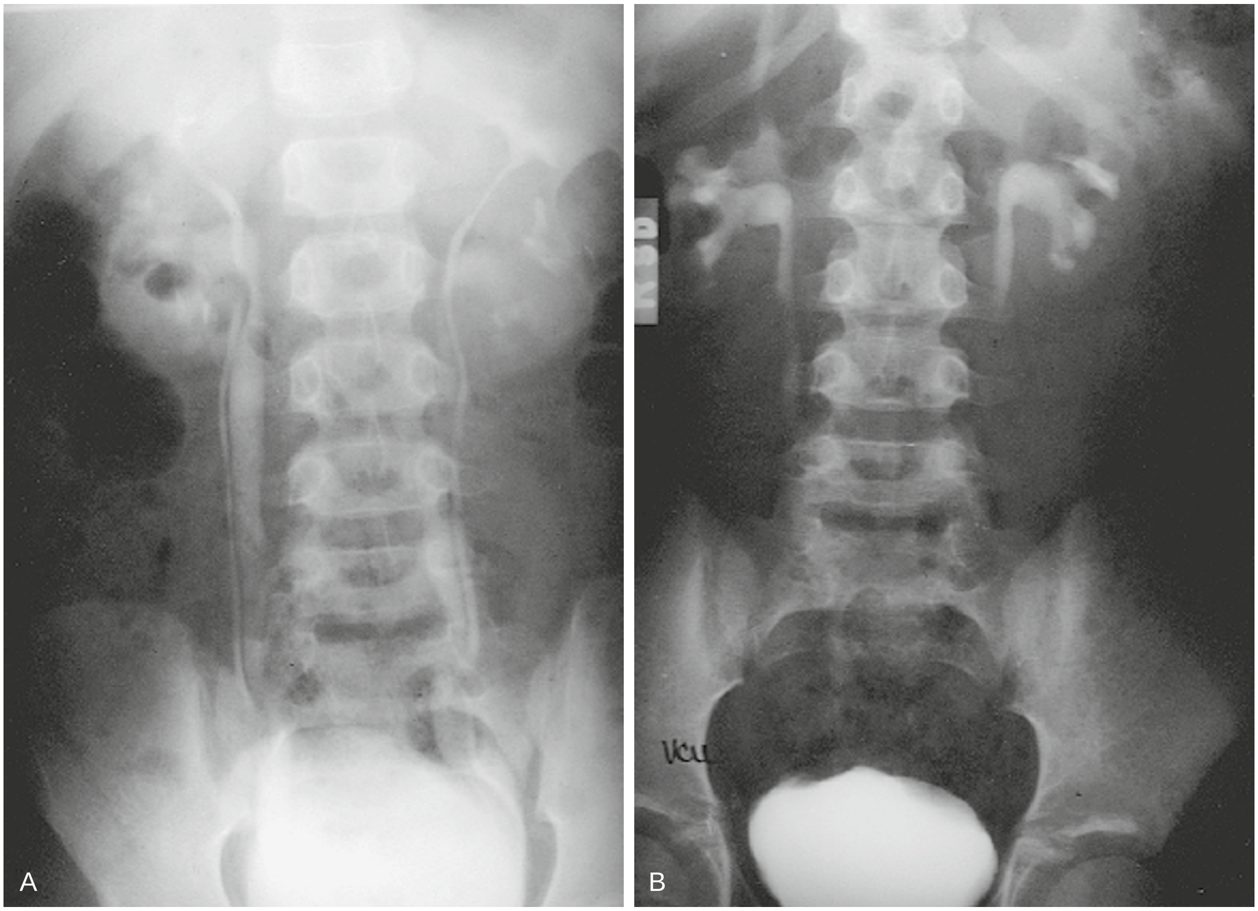


Figure 26-5 Complete ureteral duplication and vesicoureteral reflux. **A,** Intravenous pyelogram shows completed duplication of the ureters. **B,** Voiding cystourethrogram shows bilateral lower pole vesicoureteral reflux. (From Gillenwater JY, Howards SS, Grayhack JT, Duckett JW. *Adult and Pediatric Urology*. 3rd ed. St. Louis: Mosby-Year Book; 1996:2205.)

ureteral stump must be considered as discussed subsequently in this chapter.

URETEROCELES

Incidence and Diagnosis

Campbell[16] reported the incidence of ureteroceles to be 1 in 4000 (0.025%) autopsies of children, whereas Uson and colleagues[53] reported a much higher incidence of 1 in 500 (0.2%) autopsies. Ureteroceles are seen most commonly in whites and are uncommon in blacks. Ureteroceles occur four to seven times more frequently in girls than in boys.[54] Some series suggest a slight left-sided predominance, and about 10% are bilateral.[55] Of ureteroceles, 60% to 80% are ectopic, whereas intravesical ureteroceles are less common.[3,56,57] About 80% of all ureteroceles are associated with the upper pole ureter of a duplex kidney.[58] Single-system ectopic ureteroceles are rare and occur most frequently in boys; they may be associated with cardiac and genital anomalies.[59] Rarely, a ureterocele may be associated with a blind-ending ureter.[60] Associated urologic anomalies, especially the renal anomalies of fusion and ectopia, are also seen with ureteroceles. When the ureterocele arises from the upper pole of a duplex kidney, the upper pole shows evidence of renal dysplasia in about two thirds of cases.[61,62]

The most frequent presentation of ureteroceles currently is by prenatal ultrasound, although urinary infection continues to be a common presentation.[63-66] Occasionally, an infant presents with a palpable abdominal mass representing the bladder or the obstructed renal unit (Fig. 26-6). Prolapse of a ureterocele may lead to bladder outlet obstruction, which constitutes the most common cause of urethral obstruction and urinary retention in girls.[67-69] The ureteroceles that obstruct the urethra tend to "ball valve" into the bladder neck and are tense (Fig. 26-7). Because most ureteroceles are compressible during voiding, obstruction of the urethra is infrequently seen even with ectopic ureteroceles. Occasionally, a large ureterocele with an abnormally lax distorted bladder neck may lead to incontinence before or after the ureterocele is surgically treated.[70,71]

IVP had historically been the most useful study in the diagnosis of a ureterocele,[61-74] but today the diagnosis of a ureterocele relies predominantly on ultrasonography.[66,75-77] Ultrasonography typically shows a well-defined cystic intravesical mass along the posterior bladder wall (Fig. 26-8). The ultrasound appearance of a ureterocele can be deceiving, and accurate diagnosis requires analysis by an experienced radiologist. Because many ureteroceles are compressible with bladder filling, observation when the bladder is very full may miss the mucosal irregularity of the bladder base. The dilated ureter behind the bladder also may be confused with an ectopic ureter or primary obstructive megaureter. Ultrasound also can evaluate for renal parenchymal thickness and echogenicity, and the presence of a duplex kidney with upper pole hydronephrosis.

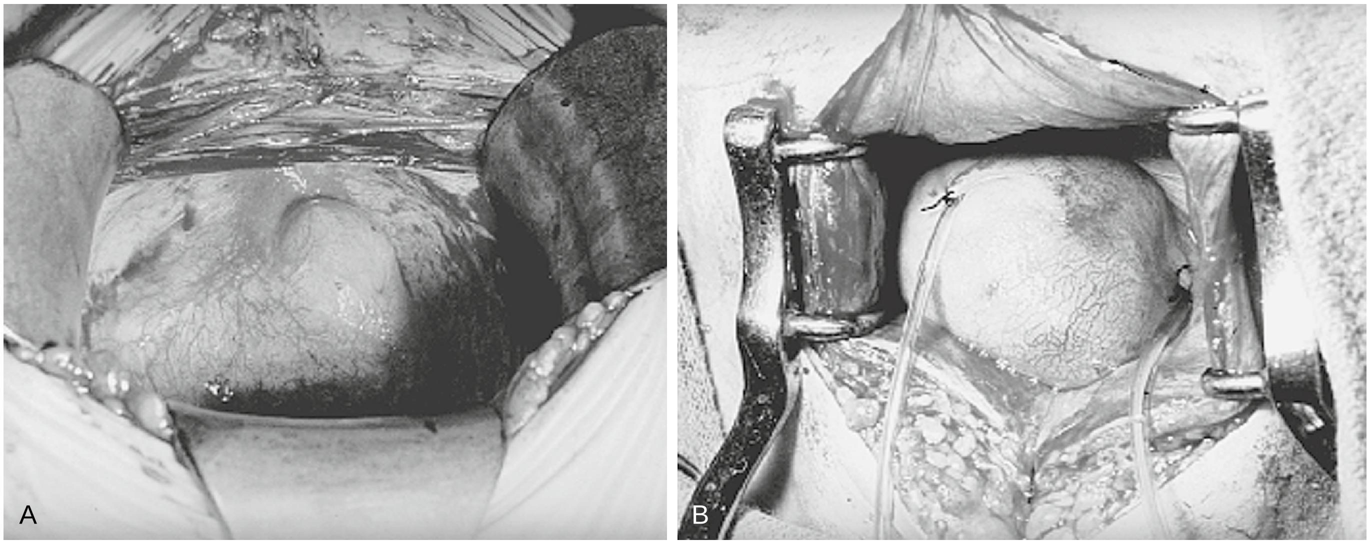


Figure 26-6 **A,** Small ureterocele. Lower pole ureteral orifice can be seen to be elevated by the ureterocele. **B,** Large ureterocele. Catheters are in the orifice of the ureterocele and ipsilateral lower pole ureteral orifice. (From Gillenwater JY, Howards SS, Grayhack JT, Duckett JW. *Adult and Pediatric Urology*. 3rd ed. St. Louis: Mosby-Year Book; 1996:2206.)

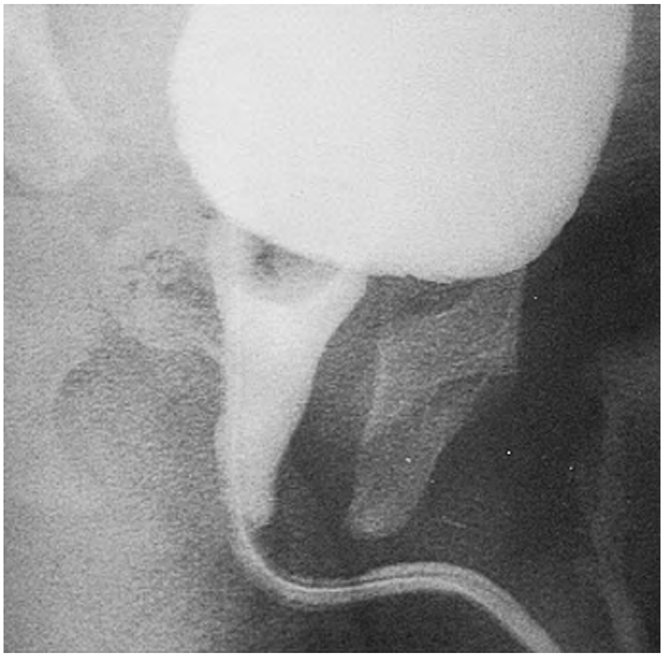


Figure 26-7 Filling defect seen from the ureterocele prolapsing into the posterior urethra.

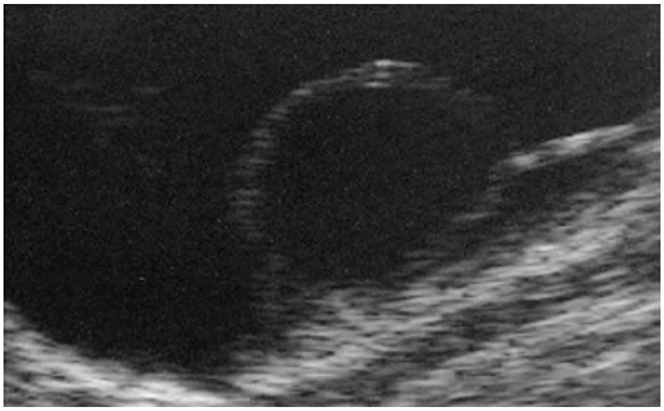


Figure 26-8 Ultrasonography shows the echogenic wall of the intravesical ureterocele.

When the associated renal unit exhibits good function, IVP shows a characteristic "cobra-head" or "spring onion" deformity of the distal ureter that is produced when opacified urine in the ureterocele is surrounded by a radiolucent halo that represents the wall of the ureterocele (Fig. 26-9). Renal function adequate to produce this characteristic image is most frequently seen with single-system intravesical ureteroceles. Of ectopic ureteroceles, 74% to 90% are associated with the upper pole of a duplex kidney that exhibits minimal or no function.[65,78] In these cases, the radiographic signs of a ureterocele are primarily negative, reflecting the displacement of the functioning lower pole renal unit and ureter by the hydronephrotic upper pole segment. The lower pole renal unit is often downward and laterally displaced, producing the characteristic "drooping lily" sign. The lower pole ureter may be tortuous and displaced away from the spine as it wraps around the dilated upper pole ureter.

At the bladder level, a negative shadow may be seen, suggesting the presence of a ureterocele. The negative shadow can vary from a large, tense, round shadow occupying much of the bladder volume to a minor irregularity along the floor of the bladder. In single-system ureteroceles, the absence of function or the presence of associated hydroureteronephrosis may help clarify the issue, but in a ureterocele associated with a duplex unit, the diagnosis may be more difficult, especially if there is little hydroureteronephrosis. The early films and the postvoid films from a urogram should be examined closely for the ureterocele because when the bladder is filled with contrast material, the ureterocele may be obscured. Intravesical ureteroceles tend to be well defined by contrast material that nearly surrounds them, as opposed to ectopic ureteroceles, which are poorly separated by contrast material from the floor of the bladder. A ureterocele may also be visualized on computed tomography (CT) scan, but CT is not routinely used for evaluation.

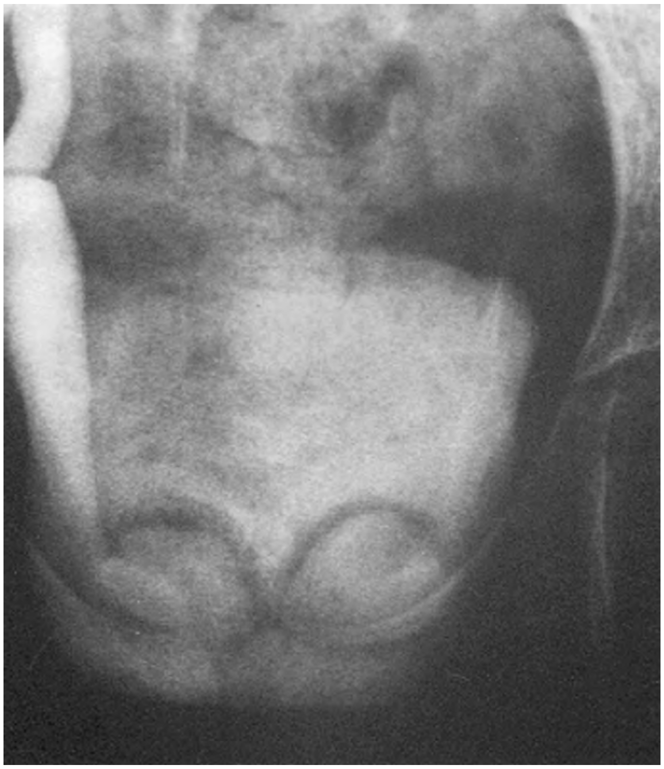


Figure 26-9 Intravenous pyelogram of bilateral single-system intravesical ureteroceles shows typical "cobra-head" deformity of distal ureter.

A good-quality VCUG constitutes a crucial component in the evaluation of all ureteroceles. With duplex ureteroceles, reflux is seen to the ipsilateral lower pole in about 50% of cases, and contralaterally in approximately 25%, and in about 10% there is reflux into the ureterocele itself.[58,65,78,79] Reflux into a single-system ureterocele is less frequent, but can occur.[78,80,81] This reflux usually occurs into a wide-mouth sphincteric, ruptured, or blind-ending ureterocele. The VCUG is also useful to ascertain the degree of detrusor backing present for the ureterocele. If detrusor support is poor, and the ureterocele prolapses through the detrusor with voiding, the ureterocele can mimic a bladder diverticulum (Fig. 26-10).[81-83] Prolapse may occur either into the dilated ureter associated with the ureterocele or through the hiatus paraureterally.[84] Occasionally, after decompression of a ureterocele, detrusor backing may seem to improve. When tense, a ureterocele may obstruct the ipsilateral lower pole ureter or contralateral ureter and the bladder outlet. Occasionally in boys, an ectopic ureterocele can prolapse toward the urethra and produce an image that may be confused with posterior urethral valves.[85]

Cystoscopic detection of ureteroceles varies and is frequently confusing. When a ureterocele is small, it may not be apparent until a peristaltic wave or flank compression causes it to fill. With very large ureteroceles, identification of any ureteral orifice in the bladder may be impossible. With a large ureterocele causing bilateral obstruction, it can be difficult to tell from which system the ureterocele originated. In this situation, a small needle wedged into the end of a fine ureteral catheter can be used to puncture the ureterocele under direct vision at cystoscopy, and injection of contrast medium may permit an intraoperative radiograph to define the anatomy. An alternative approach is to use a spinal needle passed transabdominally into the bladder and into the ureterocele under cystoscopic guidance with an intraoperative x-ray examination. A compressible ureterocele may come to resemble only a minor mucosal fold with a full bladder; one must examine the bladder carefully when it is nearly empty and when it is full. When the ureterocele has poor detrusor support and prolapses, at cystoscopy one may misdiagnose a bladder diverticulum.[86] As the bladder is emptied, and the flank is compressed, the ureterocele may fill again, permitting the correct diagnosis to be made. When the kidney is infected, flank massage may show the ureterocele orifice as pus is expunged.

Trigonal cysts are very rare, but can be confused with a ureterocele at cystoscopy.[87] Injection of contrast material into the cyst, as previously described, should help to diagnose these rare cases. Occasionally, the dilated lower end of an ectopic ureter may elevate the trigone causing a "pseudoureterocele" by ultrasound, VCUG, or cystoscopy (Figs. 26-11 and 26-12).[88] Because contralateral duplications are common with ureteroceles, it is worth every effort to assess the contralateral anatomy during cystoscopy to avoid possible damage to a ureteral orifice that was not readily apparent.

Choice of Treatment

The goals of ureterocele treatment are control of infection, protection of normal ipsilateral and contralateral units, preservation of renal function, treatment of VUR, minimization of surgical morbidity, facilitation of subsequent reconstructive procedures, and maintenance of continence. Treatment options include endoscopic decompression and numerous different surgical procedures at the kidney or bladder level. Determining which treatment approach is optimal for a child with a ureterocele is a complex aspect of pediatric urology, and many factors must be considered. Treatment must be individualized because no one approach is appropriate for all ureteroceles.

The *age of the patient* is an important consideration. Because the natural history of asymptomatic ureteroceles is unknown, the effect of any treatment options on asymptomatic neonatal ureteroceles remains difficult to determine. Antibiotic prophylaxis is started in newborns with prenatal diagnosis of ureterocele; this decreases the overall incidence of UTI. With a ureterocele detected antenatally, endoscopic incision in a newborn has the advantage of providing a simple and direct decompression of the obstructive uropathy. In the series reported from Great Ormond Street Hospital,[89] there were no cases of urosepsis after decompression. An infant may tolerate a shorter, simpler endoscopic procedure better than a more complex upper pole partial nephrectomy. If excision of the ureterocele is needed later, this is facilitated by previous endoscopic decompression.

Husmann and colleagues[90] evaluated the timing of surgical intervention, and in a nonrandomized study showed no difference in urinary infection or progressive hydronephrosis in neonates with ectopic duplex ureteroceles treated with early endoscopic treatment versus infants treated with delayed open surgery and maintained on antibiotic prophylaxis. Intervention is considered earlier, however, in the setting of breakthrough infection, renal dysfunction, or VUR. After toilet training, bladder neck surgery with ureterocele excision and bladder neck reconstruction causes a considerable degree of postoperative discomfort; treatment is best accomplished before toilet training. In older children, a "simplified" approach with an upper pole partial nephrectomy avoids bladder surgery, but is often not definitive because of associated reflux (see later discussion).[65]

The *amount of functioning parenchyma* is often considered. If a child has never had pyelonephritis, salvage of functional renal

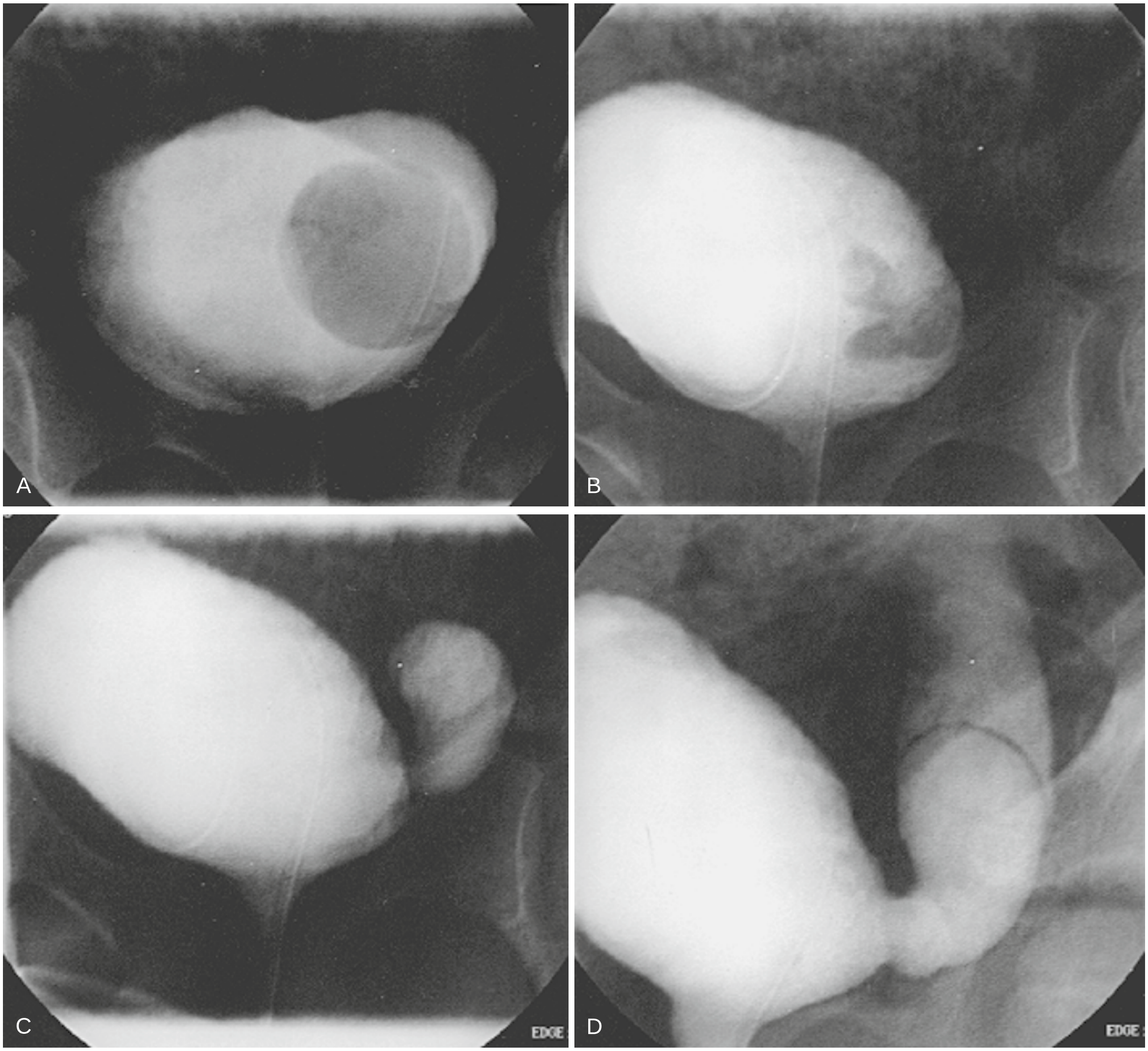
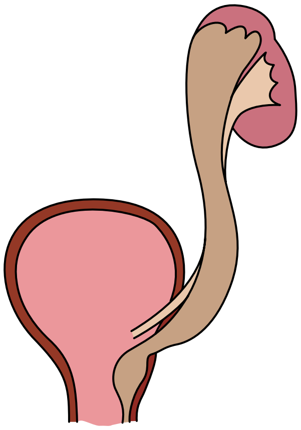


Figure 26-10 Cystograms show a large intravesical ureterocele **(A),** which prolapses through the ureteral hiatus **(B** and **C),** with subsequent reflux into the more proximal ureter **(D).**

parenchyma may be relatively more successful than in a kidney with scarring. The upper pole system associated with the ureterocele typically involves only the parenchyma subserved by the upper pole infundibulum,[24] however, which is usually less than one third of the renal function of the kidney. Upper pole nephrectomy specimens show histologic changes (fibrosis, tubular atrophy, chronic inflammation, glomerulosclerosis, dysplasia) in nearly all specimens, including moderate to severe histologic lesions in two thirds.[62] Preservation of this renal tissue should not be a paramount part of decision making. A poorly functioning renal unit drained by a decompressed ureterocele with no reflux has no routine indication for removal. Chertin and colleagues[91] evaluated poorly functioning or nonfunctioning renal moiety after endoscopic puncture, and reported 6% had a postoperative UTI, and only 4% subsequently required nephrectomy or partial nephrectomy for recurrent UTI.

A more important point is *whether the kidney is single or duplex*. Comparatively, the single system is associated with better function and less hydronephrosis, and is usually intravesical. In a single-system ureterocele, a primary endoscopic approach would seem almost always to be appropriate because open surgery would need to be directed at the bladder level. After endoscopic incision, one would have the advantage of reimplanting a smaller decompressed ureter if postendoscopic incision VUR required an open operation, which is rarely required. When the renal unit is duplex, the decision is more complex, and the issues (mentioned elsewhere in this chapter) are more critical.

The location of the ureterocele as *intravesical* or *ectopic (extravesical)* is important because the endoscopic and the open surgical reconstructions vary. Blyth and associates[92] found that at minimum 1-year follow-up, greater than 90% of



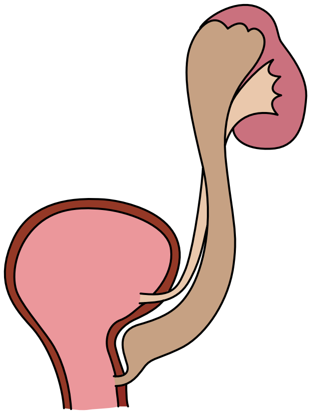


Figure 26-11 Ureterocele *(left)* and "pseudoureterocele" *(right)*. An ectopic ureter can occasionally elevate the floor of the bladder sufficiently to mimic a ureterocele. (From Gill B. Ureteric ectopy in children. *Br J Urol.* 1980;52:257.)

intravesical ureteroceles could be definitively decompressed by endoscopic incision without a need for subsequent surgery for reflux, whereas their experience with ectopic ureteroceles was much less satisfactory, with 50% of the cases requiring secondary surgery. With extended follow-up (mean 7 years) of the patients in the series by Blyth and associates, only 18% of patients with an intravesical versus 64% of patients with an ectopic ureterocele required a second operation.[93] The high percentage of second operations required in children with ectopic ureteroceles managed with initial endoscopic treatment has become well established.[93-97] Prior endoscopic decompression should permit definitive surgery to be done with one incision at the bladder level, however.[66] The decompressed ureter serving a ureterocele can be reimplanted, with the reflux resolution rate approaching that seen for ureters without a ureterocele (i.e., >90% success).

Detrusor backing is an important consideration because a poorly supported ureterocele that everts during voiding and mimics a bladder diverticulum may be more likely to require secondary reconstruction of the trigone than one that is well supported. Occasionally after ureterocele decompression, the support seems to improve, however, making it impossible to say that poor detrusor backing of the ureterocele is a firm predictor of the need for subsequent open bladder surgery.

The *degree of ureteral dilation* is also important. Occasionally, a small ureter running to a small intravesical ureterocele is noted incidentally at the time of a reimplantation for what was thought to be primary reflux, and common sheath reimplantation of the ureter from the poorly functioning upper pole with the refluxing lower pole ureter serves as very good definitive treatment.[98] If, conversely, the ureter subserving the ureterocele is massively dilated, as is more often the case, attempts at reimplantation of such a system would be fraught with a greater complication rate. After endoscopic decompression, the ureteral dilation would greatly diminish, improving reimplantation results.

Associated VUR seems to be the most important predictor of the need for open surgery and emphasizes the importance of the VCUG. If high-grade reflux is associated with a ureterocele, a primary endoscopic incision facilitates subsequent surgery at the bladder level if necessary by decompression of the ureterocele.[66] If there is no VUR, a simplified approach by an upper pole partial nephrectomy for an ectopic ureterocele is a reasonable treatment option because there is less concern over a residual reflux ureteral stump. With ectopic ureteroceles, the absence of associated reflux is rare. In a review by Husmann and coworkers,[71] it is readily evident that reflux was the major factor leading to the need for subsequent surgery after an upper pole partial nephrectomy to decompress a ureterocele. If no reflux was present, none required additional bladder level surgery. If grade I or II reflux was present in only one ureter, 40% of patients required further surgery; in contrast, higher grade reflux into one or more renal moieties regularly led to further surgery (96%).

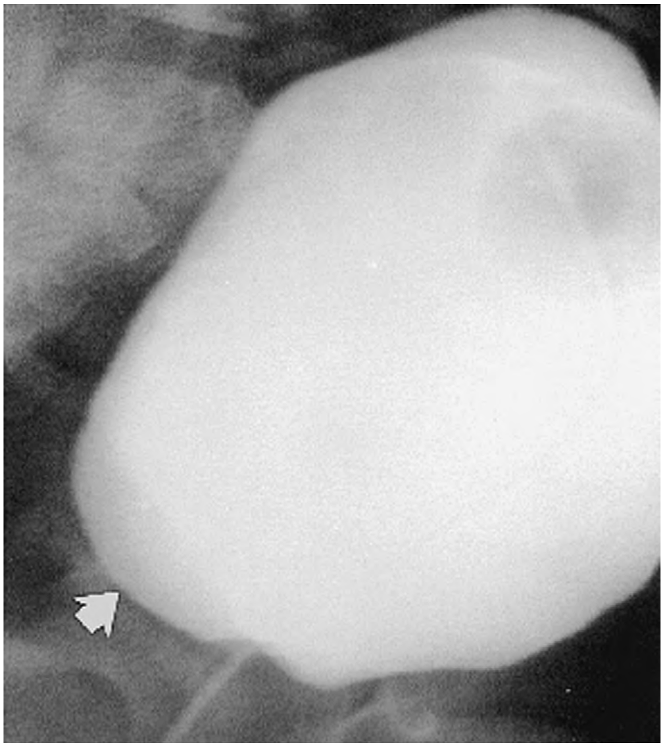


Figure 26-12 Patient with a right upper pole ectopic ureter creating a pseudoureterocele *(arrow)*.

Nonoperative management has been proposed by some authors in selected cases, including prenatally detected ureteroceles associated with multicystic dysplasia without VUR.[99] Han and coworkers[100] used MAG-3 renography to identify 13 patients with nonobstructed ureteroceles or nonfunctional renal moiety who were managed without surgical intervention with median follow-up of 3.4 years, and surgery was subsequently necessary in 31% (progressive obstruction in 1 patient and breakthrough urinary infection in 3 patients). Further data are required on watchful waiting of ureteroceles before this can be recommended.

Treatment of Intravesical Ureteroceles

Intravesical ureteroceles associated with a single ureter are more commonly seen in adults and older children, and this may be an acquired phenomenon.[101] Although obstruction and hydroureteronephrosis are more severe in children than in adults,[102] single-system ureteroceles usually are associated with better function and less hydronephrosis than duplex renal units and their more frequently associated ectopic ureteroceles. For single-system ureteroceles, a primary endoscopic approach seems advisable in almost all cases. Even if iatrogenic reflux were to follow, the decompressed ureter would be an easier one to reimplant later.

Endoscopic decompression of ureteroceles was suggested initially in 1962 by Zielinski[103] and shortly thereafter by Hutch and Chisholm.[104] Tank[105] advocated unroofing of ureteroceles primarily for relief of obstruction without regard for reflux, and found that 50% showed such improvement in function on IVP that subsequent nephrectomy was not thought necessary, and lower tract reconstruction for recurrent infections was required in only 10% of cases. The prior endoscopic approach was to perform a high incision, however, and the presence of postoperative reflux was common. The current approach to ureterocele decompression is a small puncture placed low on the ureterocele to preserve a flap valve of the collapsed ureterocele and prevent reflux, as suggested by Monfort and colleagues[106,107] and Blyth and associates.[92] Historically, acceptance of ureterocele excision was slowed because of concerns over definitive relief of obstruction and concern for inducing iatrogenic reflux. Clinical series have shown successful decompression of intravesical ureteroceles in greater than 90%, however, and induction of iatrogenic reflux in only 6% to 32%.[66,93,94,97] It is evident from the results with intravesical ureteroceles that greater than 80% of patients may be adequately treated by endoscopic incision alone.[92,94,97] For intravesical ureteroceles, whether associated with a single or duplex renal unit, the advantage of a primary endoscopic approach seems to be well recognized.

Several technical points concerning endoscopic treatment of ureteroceles may improve outcomes and decrease complications. Because many ureteroceles are compressible with bladder filling, it is often helpful to keep the bladder empty and massage the flank to distend the ureterocele to ensure a low incision on the front wall of the ureterocele just above the bladder neck. A 3F Bugbee electrode with the cutting current at a level high enough to ensure a clean puncture is used. Although a low incision is preferred in efforts to create a flap-valve mechanism of the decompressed ureterocele, if one incises too low, the incision may potentially be below the level of the ureterocele floor. A very small 3F hole is adequate in most cases because the thermal injury of the incision leads to a further enlargement in the hole. If the ureterocele appears to be very thick walled, a slightly larger incision may be appropriate.[66]

Follow-up after an endoscopic incision initially involves a renal and bladder ultrasound scan at 1 month after the procedure. Although residual hydroureteronephrosis often persists, a diminution of some degree indicates that decompression has been achieved. Subsequent imaging of the upper tracts and a VCUG 6 months after the procedure help direct further treatment.

In the open reconstruction of ureteroceles, if there is poor detrusor backing for the ureterocele, the bladder wall must be repaired at the time of ureterocele excision. In single-system ureteroceles that are decompressed, the degree of ureteral dilation decreases enough that at the time of reimplantation a 5:1 ratio of submucosal tunnel length to diameter can be achieved to prevent VUR in most cases without ureteral tailoring. With significantly dilated ureters associated with ureteroceles, sometimes even after decompression, a tailored reimplant may be required. Cohen's[108] technique of cross-trigonal advancement generally permits the reimplant to be done away from the area of bladder wall reconstruction. Occasionally, renal function is very poor, and a primary nephrectomy may be justified to remove a destroyed renal unit. As in adults, occasionally a single-system ureterocele is small with minimal obstruction and requires no treatment.

When an intravesical ureterocele is associated with the upper pole of a duplex kidney, the upper pole often exhibits poor function, and an upper pole partial nephrectomy with partial ureterectomy to below the level of the iliac vessels may be performed as described for ectopic ureteroceles in the following section. This approach is particularly attractive when there is no VUR because this "simplified" approach is likely to permit the avoidance of any bladder-level surgery.[71] The incidence of VUR after endoscopic incision of intravesical ureteroceles is sufficiently low (see earlier discussion), however, to make the endoscopic approach perhaps even more attractive in treatment of an intravesical ureterocele in a duplex system.

At partial nephrectomy, the ureter associated with the decompressed ureterocele is usually left open and drained if no reflux is present preoperatively. Intraoperatively, attention must be paid to avoid damage to the lower pole ureter. An intravesical ureterocele as part of a duplex unit may be associated with adequate function and a ureter small enough (especially after endoscopic decompression) to permit ureterocele excision and a common sheath reimplant of the two ureters. Occasionally, the associated ureter is too dilated to be reimplanted without tailoring. If there is no reflux driving surgery at the bladder level, and if upper pole function justifies salvage, a renal-level ureteroureterostomy or ureteral pyelostomy may be employed effectively. The distal upper pole ureter in these salvageable cases is handled as previously discussed.

Treatment of Ectopic Ureteroceles

Ectopic ureteroceles are most commonly associated with the upper moiety of a duplex kidney and can be treated by many different surgical procedures. In clinical series, the endoscopic treatment of ectopic ureteroceles has not been as successful for definitive treatment as for intravesical ones, with successful decompression of ectopic ureteroceles in 67% to 96%.[40,66,92-95,97,109,110] Induction of iatrogenic reflux in the clinical series occurred in 27% to 56%, with a higher incidence when laser incision was used.[111] The incidence of secondary surgery after endoscopic procedures has been reported to be approximately 50% to 80%.

Despite the frequent need for an open surgical procedure after the endoscopic approach, the simplicity and minimal invasiveness of this technique are advantageous in neonates. Even if reflux were to follow an endoscopic procedure, the likelihood of urosepsis is very slight.[89] If, as is common, associated reflux necessitates open bladder-level surgery, reconstructive surgery can be electively carried out between 1 and 2 years of age, when complicated reconstructive procedures at the bladder neck are more safely accomplished and better tolerated than if one waits until after the age of toilet training. The decompressed ureter to the ureterocele can usually be successfully reimplanted, and upper pole partial nephrectomy, even for a poorly functioning upper pole, is rarely needed. Gran and coworkers[112] reviewed children with nonfunctioning renal moieties associated with obstructing ureteroceles who were treated with lower urinary tract reconstruction (ureteral reimplantation, ureteral excision, and bladder neck reconstruction, in which 81% had a prior endoscopic ureterocele excision), and reported excellent results with no patients requiring additional upper tract surgery at a mean follow-up of 5 years.

Endoscopic incision of an ectopic ureterocele differs technically from incision of an intravesical ureterocele. Achieving decompression of the ureterocele still requires a good, clean puncture with maintenance of a flap valve to prevent reflux; a low puncture of the ureterocele so as to maintain a flap valve is important and commonly accepted.[40,95,113] The treatment of the urethral extension of an ectopic ureterocele has raised concern that an obstructing distal tongue might remain after decompression. Schlussel and associates[113] and Smith and coworkers[95] reported no problems, however, with the urethral extension of the ureterocele after puncture at the intravesical level only. Care was taken to make a small low transverse incision that was within the bladder with the bladder neck closed. Technically, this incision can be accomplished by sweeping the cystoscope along the bladder wall from lateral to the ureterocele to medial and picking up the edge of the ureterocele just inside the bladder neck. An angled Bugbee electrode facilitates a puncture perpendicular to the ureterocele wall. If the ectopic ureterocele is decompressed by intravesical puncture, the urethral extension is usually adequately decompressed and unlikely to cause any difficulty. Concern about a distal residual cusp of the ureterocele may be more relevant to open ureterocele excision when the urethral extension could remain as a cusp, catching urine during voiding and obstructing the urethra similar to an anterior urethral valve.

The traditional treatment of an ectopic ureterocele associated with a duplex renal unit used to be “total reconstruction,” with a combined approach of a bladder operation with ureterocele excision, detrusor reconstruction, and reimplantation of the ipsilateral lower pole ureter followed by a separate flank incision for an upper pole partial nephrectomy.[114,115] If the upper pole had questionable function, or the child was sufficiently ill to warrant a staged approach, the upper pole ureter could be exteriorized temporarily as a cutaneous ureterostomy. Monfort and colleagues[107] used this technique in 18 patients with recovery of significant function in only 17%, indicating that this approach is rarely useful.

Because most ureteroceles manifest in very young patients, often less than 1 year of age, the total reconstruction approach requires a technically challenging excision of a large ureterocele, often with a urethral extension. Complications with this procedure are common.[116] As mentioned previously, a lip of the urethral extension of an ectopic ureterocele may act as a urethral valve and produce bladder outlet obstruction. Also, if the ureterocele is excised, but the bladder neck is imperfectly reconstructed, incontinence may follow.[70] Incontinence also can rarely result from incomplete excision of a ureterocele that has an orifice beyond the sphincter mechanism, leaving a channel that bypasses sphincteric control.[117] Proponents of this approach note that most children may be treated with one operation, albeit with two incisions. In one series, only 14% of children with ectopic ureteroceles who underwent total reconstruction required subsequent intervention, all because of persistent VUR.[41]

Because of the potential complications secondary to “total reconstruction” early in life, an alternative upper tract or “simplified approach” for ureteroceles was developed. In duplex renal units with an associated ectopic ureterocele, the upper pole unit usually has not exhibited sufficient function to warrant salvage.[78,118] Because of this, a simplified approach, based on a primary upper pole partial nephrectomy with ureterocele decompression and later a staged approach to bladder-level surgery if required, was attempted at several institutions.[65,119-121] The upper pole ureter was excised down to the level of the iliac vessels and left open to facilitate decompression of the ureterocele. The expectation was that decompression would simplify bladder surgery when the child was older, or possibly could eliminate the need for an operation at the bladder level completely. Ureterocele decompression by this technique had the additional benefit that ipsilateral and contralateral reflux or obstruction or both would frequently subside. The ureterocele generally collapses so completely that it is difficult to visualize subsequently on VCUG.[65,120,122,123]

In the series by Husmann and coworkers[71] assessing the results of partial nephroureterectomy alone, the grade of preoperative reflux seemed to be an important predictor of the need for further surgery. If less than grade III reflux was present into the ipsilateral lower pole ureter or the contralateral ureter, 60% of their cases required no further surgery with spontaneous resolution of the reflux. A higher grade of reflux resulted in a 96% subsequent surgery rate for reflux, however. In a more recent series, Husmann and colleagues[97] noted that 30% of children without reflux developed reflux after partial nephrectomy; half of these children spontaneously resolved their reflux, whereas the other half required additional surgery for reflux. Other series have found the overall need for eventual bladder surgery to range from 25% to 50%.[65,120,121] Although the simplified approach of an initial upper pole partial nephrectomy provides effective decompression, an incidence of subsequent bladder-level surgery is likely to be significant, especially if initial high-grade reflux is present.

The 1995 report by Husmann and coworkers[71] noted a rare complication of the simplified approach. Six percent of patients treated with upper pole partial nephrectomy alone developed stress urinary incontinence after toilet training. In these cases, the mass of the distended ureterocele may have distorted the bladder neck sufficiently to cause incontinence after decompression.

Experience with the simplified approach suggests that this approach to the treatment of ectopic ureteroceles with duplex systems permits most children without reflux to avoid a secondary bladder procedure. It is rare with ectopic ureteroceles to have no reflux, however. As with endoscopic decompression of the ectopic ureterocele, most children with reflux treated by the simplified approach require a second operation at the bladder level.[71,97] The significant need for lower tract reconstruction has led some authors to suggest that in older children, complete reconstruction may be a more definitive and efficacious treatment modality.[97]

The advent of laparoscopic heminephroureterectomy presents another operative alternative that in experienced hands may be selected in this group of children.[124] Benefits of the laparoscopic approach include less invasive procedure, magnification, excellent visualization, minimal blood loss, smaller scar, and faster recovery, whereas negative aspects include a substantial learning curve, operative time, and concern over the safety of the retroperitoneal approach in children younger than 1 year of age.[125,126] It is our view, however, that with primary endoscopic incision, it should be possible to carry out definitive open surgery with one procedure at the bladder level. Poor function of the upper pole does not require that it be removed. In the very rare cases in which the upper pole function is good, and there is no initial VUR present, a ureteropyelostomy or high ureteroureterostomy may be a preferable alternative; however, this approach is less suitable if the lower pole pelvis is intrarenal, or the lower pole ureter is nondilated. In that case, the small amount of function represented in the upper pole would be better removed than to jeopardize most of the renal function coming from the lower pole. Efforts at parenchymal salvage can be especially rewarding in small infants because recovery of function can occasionally be remarkable.[127]

An alternative treatment of upper tract preservation has been attempted with a primary bladder-level operation involving excision of a nondecompressed ureterocele and a common sheath reimplantation, but this has the disadvantage of requiring the reimplant of an often very dilated ureter into the small bladder of an infant. Amar and associates[128] suggested excision of a ureterocele, lower pole ureteral reimplantation, and a low ureteroureterostomy of the upper pole ureter into the lower pole ureter. A disadvantage of this approach is the possible development of ureter-ureter reflux. Endoscopic decompression followed by an open operation at the bladder level with a duplex reimplant may be preferable.

Occasionally, a surgeon begins a ureteral reimplantation for what seems to be simple primary VUR into a single system, and as the ureter is mobilized a second small ureter is found running to a small nonobstructed ureterocele. The small size of the ureter and associated lack of function in the diminutive upper pole unit may lead to this intraoperative discovery.[98] Although there is minimal function in the upper pole unit, treatment is usually satisfactory by a common sheath reimplant. It is uncommon to need to remove the upper pole renal unit later.

Sometimes an ectopic ureterocele from the upper pole of a duplex kidney causes such a degree of lower pole obstruction or reflux that the lower pole is functionally destroyed. It has not been our experience that decompression of the ureterocele results in much return of function in the lower pole. In this situation, a primary total nephroureterectomy is justified.

There are several technical points when performing an upper pole partial nephrectomy to treat a ureterocele in a duplex renal unit. A relatively short transverse flank incision just below the tip of the 12th rib permits complete mobilization of the kidney to facilitate surgery on the upper pole. Because the upper pole renal vasculature is often anomalous and variable,[129] care should be taken to identify the small vessels that frequently course directly into the upper pole. If dissection is kept close to the upper pole, vessels running to this unit can be clearly identified before their division, which reduces the chance of damaging the blood supply to the lower pole. The ureter to the upper pole usually runs posterior to the renal vessels, and no attempt is made to dissect out the hilar vessels. Occasionally, an aberrant vessel is located behind the ureter. After identification and division of the ureter to the upper pole, gentle traction guides dissection of the upper pole parenchyma. The upper pole capsule may be stripped back for later use in closure if not too adherent from previous inflammation.

Complete removal of the upper pole collecting system is the most important aspect of an upper pole partial nephrectomy. We make the parenchymal incision just on the upper pole side of the line of demarcation from the lower renal unit, which is usually evident after the division of the upper pole vessels. The hypoplastic or dysplastic upper pole can then be excised. Manual compression of the kidney provides adequate vascular control, and blood loss should be minimal.

Next, the distal end of the upper pole ureter should be dissected down to below the level of the iliac vessels, where it begins to assume a common adventitial sheath with the lower pole ureter. The upper pole ureter is usually dilated and tortuous, and frequently appears to wrap around the lower pole ureter. Dissection kept immediately on the wall of the upper pole ureter prevents injury to the lower pole ureter. After dissection reaches the level of the iliac vessels, which is not difficult through the usual flank incision, the upper pole ureter is opened, and the interior of the ureterocele is gently irrigated with a feeding tube. If there is no reflux into the ureterocele, the stump of the excised upper pole ureter is left open.

Occasionally, when the ureterocele is a large one, a small feeding tube may be left in the lumen of the upper pole ureter extending down into the ureterocele for several days to act as a wick to help ensure that the ureterocele does collapse. If reflux into the ureterocele has been noted to be present, the upper pole ureter should be ligated. Here, there is an increased likelihood that a subsequent bladder operation to remove the ureterocele and upper pole ureteral stump may be required when the child is older. A small Penrose drain left in the area of the ureteral stump and one in the area of the removed upper pole renal parenchyma provide drainage.

In children who require ureterocele excision and lower pole ureteral reimplantation, it is usually delayed electively until the child is about 2 years old, and is most commonly needed for persistent ipsilateral lower pole or contralateral reflux. Ureterocele excision and bladder neck reconstruction are considerably more symptomatic than a simple ureteral reimplant, and it is preferable to perform the surgery before the age of toilet training. Several technical points are pertinent. There are two basic methods for the intravesical excision of a ureterocele. If the detrusor backing for the ureterocele is solid, the back wall of the ureterocele can be left in place and the lower pole ureter tunneled beneath the mucosa. Usually a bladder wall reconstructive procedure is warranted by detrusor weakness behind the ureterocele, however. This may reflect an embryonic abnormality of the trigone, especially with ectopic ureteroceles (DA Canning, personal communication, 2000).

It is usually possible to save a portion of the side walls of the ureterocele by separating the inner lining of the ureterocele, which permits later mucosal coverage of the area of bladder wall reconstruction. If the ureterocele has a urethral extension, it is important not to leave a distal lip of mucosa that can be an obstructing valve. The entire urethral tongue of ureterocele can be excised and the bladder neck area carefully reconstructed before closing the mucosa, or if the bladder neck and urethra have not been dilated by the ureterocele, merely removing the ureterocele roof as it extends down the urethra suffices. The latter is technically a simpler procedure, but one must be certain that a functionally intact urethra and bladder neck are left behind because the primary reconstruction of these structures is easier than a secondary approach. In the series by Husmann and coworkers,[71] 6% of the girls treated by an upper pole partial nephrectomy developed urinary incontinence only after puberty, presumably as a result of a persistent weakening of the bladder neck by the ureterocele after decompression.

To reconstruct the bladder neck defect after ureterocele excision, the technique of "keeling" as described by Stephens[2] is particularly attractive. A series of sutures is used to evert the detrusor ("keeling") until the bladder neck is reconstructed to a normal diameter. The mucosal edge of the ureterocele provides a good guide to the amount of eversion needed. When the mucosa is reapproximated at the bladder neck, good bladder neck reconstruction can be ensured.

If a bladder-level operation is needed after endoscopic incision of a ureterocele, it usually is for reflux associated with ectopic ureteroceles. A clear advantage of the endoscopic incision is that the decompressed ureter usually shrinks in diameter sufficiently to permit reimplantation into the bladder, with results approaching those for normal refluxing ureters.[66] Poor function of an associated upper pole renal segment alone is not an indication for a partial nephrectomy, as when there is no associated persistent obstruction or reflux, and follow-up has not revealed clinical problems.

When operating at the bladder level for persistent reflux after upper pole partial nephrectomy (simplified approach), as the ureterocele is dissected the upper pole ureteral stump is mobilized with the lower pole ureter. This dissection in most cases can be accomplished intravesically. After the lower pole ureter has been sufficiently mobilized for an adequate reimplant, the upper pole ureteral stump is opened on its wall opposite the common one shared with the lower pole ureter. No effort is made to excise the portion of the wall of the upper

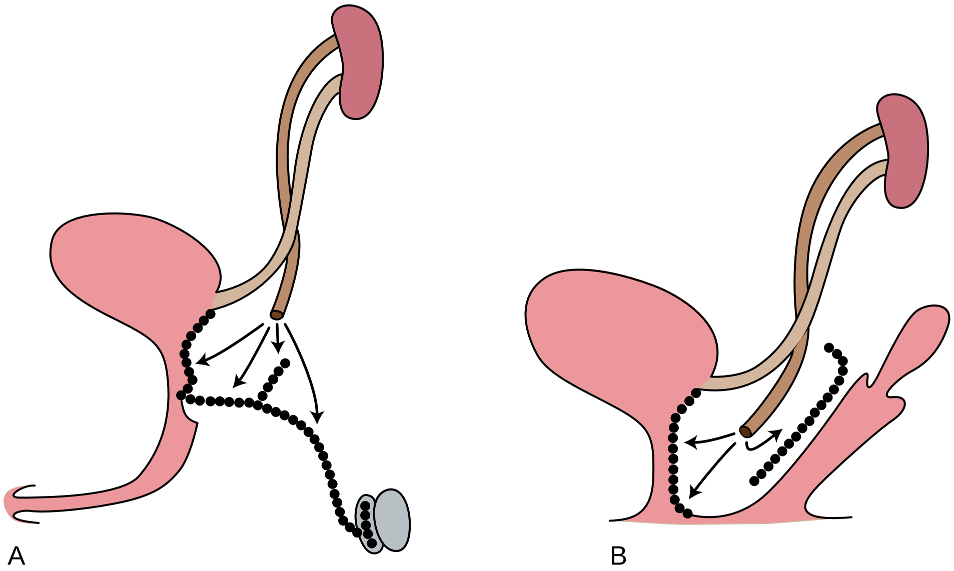


Figure 26-13 **A,** Ureteral ectopia in the male. Possible sites of ectopic ureter are above the external sphincter. **B,** Ureteral ectopia in the female. Ectopic ureter may be located beyond the continence mechanism and produce incontinence. (From Johnston JH. Problems in diagnosis and management of ectopic ureters and ureteroceles. In: Johnston JH, Scholtmejer RJ, eds. *Problems in Pediatric Urology.* Amsterdam: Excerpta Medica; 1972:57.)

pole ureter that is contiguous with the lower pole ureter. In this way, there should be minimal risk of injury to the lower pole ureter. A Cohen cross-trigonal reimplant is usually feasible and keeps the course of the ureter away from the area of recent bladder wall reconstruction. A ureteral stent is used only if the lower pole ureter is significantly abnormal.

ECTOPIC URETER

Incidence of Single and Duplex Systems

A ureteral bud with an abnormally high origin from the mesonephric duct may result in an ectopic ureter opening at the bladder neck or more caudally (see embryology section earlier in this chapter). There are multiple possible sites for an ectopic ureter in boys (always above the external urethral sphincter) and girls (Fig. 26-13). In autopsy series, the incidence of ectopic ureters is 1 in 1900 (0.05%).[16] Ectopic ureters are much more common in girls, with only about 15% of ectopic ureters occurring in boys.[130] In 80% of all ectopic ureters, the ureter is attached to the upper pole of a duplicated renal system. The percentage of ectopic ureters associated with duplication in girls is even higher than 80%; however, in boys, an ectopic ureter drains a single system more commonly.[131,132] About 10% of ectopic ureters are bilateral.[133] When an ectopic ureter is part of a duplex system, the contralateral system is duplicated in about 80% of cases, and 21% of these have contralateral ectopy as well.[134]

Renal hypoplasia or dysplasia constitutes the most frequently encountered anomaly associated with an ectopic ureter. Generally, the degree of ureteral ectopy away from the bladder correlates with the degree of renal abnormality, although this correlation is more apparent for duplex systems than for single systems.[135] Severe ectopy with an orifice in the genital system is almost always associated with nonfunctioning renal tissue.[130,136] Some series have shown a higher incidence of other associated anomalies, especially imperforate anus, in single-system ectopy than in duplex ectopy.[88]

A single ectopic ureter with a normal contralateral system usually does not result in any deficiency of the bladder neck, and continence is intact. When two single ureters are ectopic, however, the bladder neck fails to form normally, resulting in severe urinary incontinence. When one single ectopic system is at the bladder neck, and one is more distal, an intermediate level of bladder neck abnormality is present, and most children in this group are continent.[137]

Ectopic Ureter in Girls

The fundamental gender difference in ureteral ectopy is that in girls the ectopic ureter can terminate at a level distal to the external sphincter and cause incontinence.[138,139] About one third of ectopic ureters open at the level of the bladder neck or slightly more distally in the proximal urethra (Fig. 26-14).[140] With a higher orifice, there is a lower chance of associated urinary incontinence; however, obstruction is more common because a higher ectopic ureter traverses a greater portion of the musculature of the bladder neck and drains only during voiding when the continence mechanism is open. VUR occurs in 75% or more of these higher ectopic ureteral orifices, producing the paradox of reflux and obstruction. By having the bladder neck repeatedly open, the cyclic VCUG of Lebowitz and Wyly[141] provides an opportunity for the obstructed ectopic ureter to drain before contrast material is voided, and increases the likelihood that the contrast material will reflux into the ectopic system. When the ectopic ureter enters at the level of the external sphincter or lower, reflux is less commonly present.

One third of ectopic ureters in girls terminate in the area of the vaginal vestibule immediately around the urethral orifice. This area marks the terminal end of the Gartner duct, the mesonephric duct remnant in the female. Occasionally, infant girls present with an ectopic ureter entering what appears to be a urethral diverticulum, but which is actually a Gartner duct cyst.[142] In about 25% of ectopic ureters in girls, the orifice opens into the proximal vagina. More rarely, an ectopic ureter can end at a higher site along the course of the Gartner duct with an opening at the level of the cervix or uterus (<5%). These uterine, cervical, or vaginal cases presumably result from rupture of the Gartner duct into the urovaginal canal along their

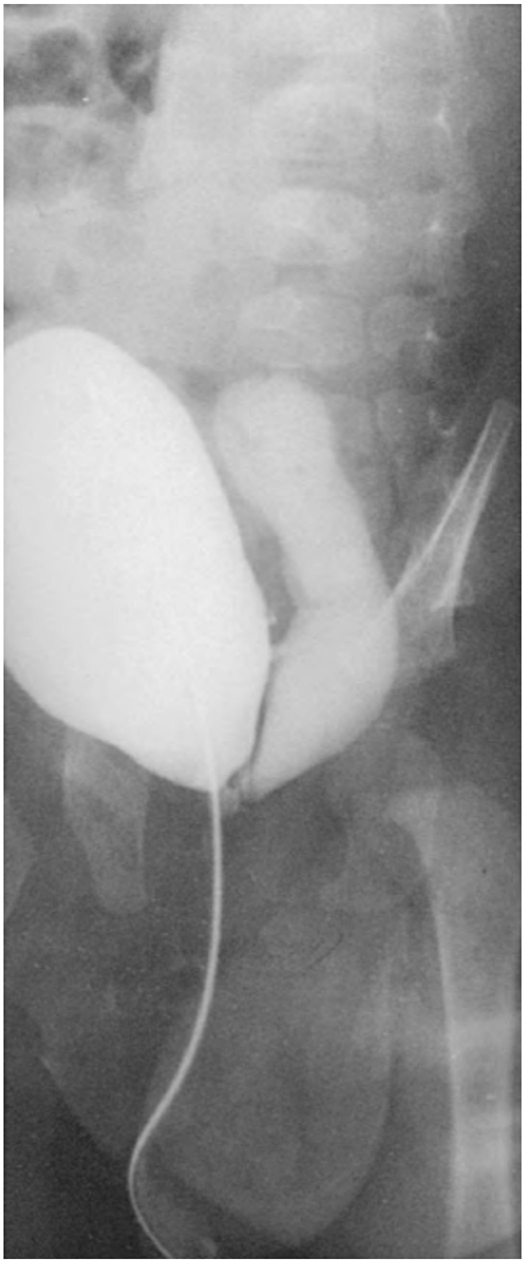


Figure 26-14 Cystogram shows ectopic ureter entering at the bladder neck. (From Gillenwater JY, Howards SS, Grayhack JT, Duckett JW. *Adult and Pediatric Urology*. 3rd ed. St. Louis: Mosby-Year Book; 1996:2222.)

common wall. Ureteral ectopy into the rectum is very rare, but has been reported.[143]

About one half of girls with ectopic ureter present with a classic history of continuous dribbling incontinence despite what seems to be a normal voiding pattern.[130,134,135] Sometimes, parents may not note the abnormal character of continuous incontinence in a preschool-aged girl, and commonly the problem in the female goes unrecognized until adulthood.[144] If the associated ureter is very dilated, the child may be continent when supine, and the pattern may be daytime wetting erroneously suggestive of stress incontinence or overactive bladder. Occasionally, the presentation consists of a persistent foul-smelling vaginal discharge. If the ureter ends in a Gartner duct cyst, the child may present with a mass on the anterior vaginal wall. When the ectopic orifice is quite high, and there is significant obstruction or reflux or both, urinary infection is frequent and is the most common presentation for an ectopic ureter in a small child. The evaluation of prenatal hydronephrosis is another form of presentation.[145] An infant may present with an abdominal mass resulting from a severely obstructed ectopic ureter.[142] There are well-documented cases of girls with ectopic ureters entering the vestibule or distal urethra without incontinence, presumably owing to obstruction of the ureter as it traverses the continence mechanism with emptying only during voiding.[146]

The diagnosis of an ectopic ureter in a girl may be very difficult. With ectopy into the external genitalia, the associated renal unit is likely not to be visualized on IVP.[147] Ultrasound may be especially useful, detecting the dilated ectopic ureter behind the bladder. If there is little hydroureteronephrosis of the ectopic upper pole system, diagnosis may depend on recognizing the absence of an upper pole calyx or an apparent excessive thickness of the renal tissue on the medial aspect of the upper pole. Tomography during IVP, computed tomography, or renal scintigraphy may aid in making this diagnosis.[148,149] Magnetic resonance imaging (MRI) has been used to delineate the fluid-filled ureter and its anatomy.[150] Bilateral ectopic ureters occur in about 10% of cases, and diagnosis frequently requires a high index of suspicion.[133]

If the ectopic ureter is single and beyond the continence mechanism, the associated renal tissue frequently is nonfunctional, and the diagnosis may be rendered even more difficult by the fact that the associated kidney itself may be ectopic or even crossed and fused.[151] Renal function may be inadequate to permit visualization by either IVP or renal scan.[152] The finding of a hemitrigone at cystoscopy may lead to the erroneous diagnosis of renal agenesis. Associated genital and anal anomalies occur in about one third of cases,[153] and may mask the presentation of single ectopy. Ultrasound used to detect a dilated ureter behind the bladder may be particularly useful in this situation.[154] Vaginograms carried out by occluding the introitus with a Foley balloon may show reflux into a vaginal ectopic ureter. The ectopic ureter alternatively may be visualized at vaginoscopy. There are cases, however, in which exploratory surgery is required to look just above the bladder for the ureter. When found, the ureter can be traced upward to its associated renal unit.

Physical examination with close observation of the area around the urethral meatus and distal vagina may reveal a recurring drop of liquid over a very small opening that can be probed and retrogradely injected to confirm the location of an ectopic ureter (Fig. 26-15). The presence of an ectopic ureter may be suggested if the bladder is filled with indigo carmine–stained or methylene blue–stained saline solution via a Foley catheter, and observation of the perineum reveals a continued slow drip of clear urine. Phenazopyridine hydrochloride (Pyridium) seems to be a better color marker excreted by poorly functioning renal tissue than methylene blue or indigo carmine,[151] and if a cotton swab is left high in the vagina overnight and stains orange, it suggests the diagnosis of a vaginally ectopic ureter. Vaginoscopy with attention to the superior lateral aspect of the vagina may reveal the vaginal ectopic ureter. Exerting pressure on the anterior vaginal wall may produce a jet of cloudy fluid or pus from the ectopic orifice, revealing its presence.

The surgical treatment of an ectopic ureter in a girl depends on the associated ipsilateral renal function. A single-system ectopic ureter to the genital system usually has poor function, and a nephroureterectomy is appropriate, either by an open or by a laparoscopic approach.[155] With single-system ectopic ureter to the bladder neck or urethra, the function may justify

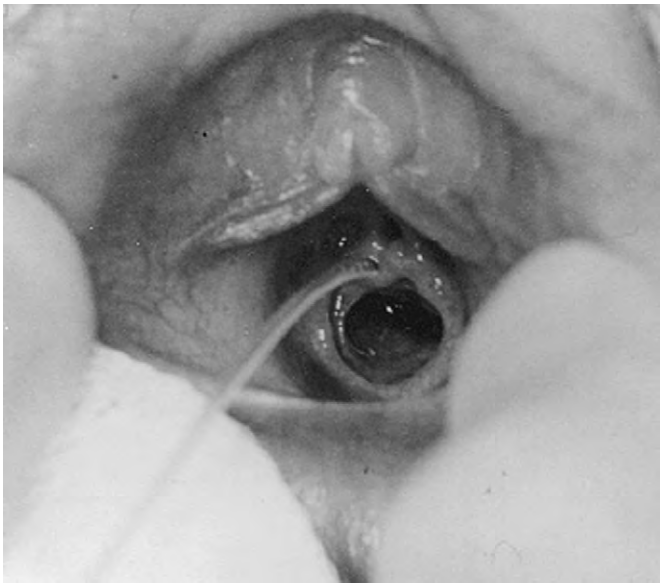


Figure 26-15 Ectopic ureter in vaginal vestibule is shown with a ureteral catheter inserted.

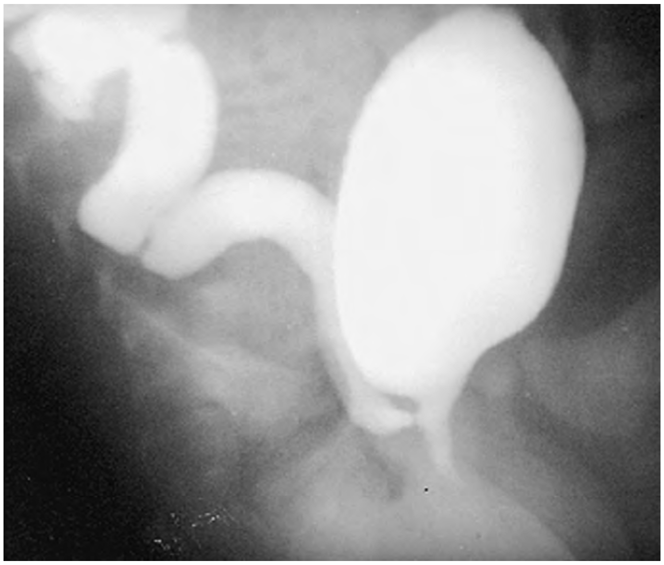


Figure 26-16 Cystogram shows ectopic ureter to the posterior urethra in a boy presenting with infant sepsis. (From Gillenwater JY, Howards SS, Grayhack JT, Duckett JW. *Adult and Pediatric Urology*. 3rd ed. St. Louis: Mosby-Year Book; 1996:2226.)

a reimplantation of the ureter into the bladder.[135] Endoscopic injection with dextranomer/hyaluronic acid for VUR of an ectopic ureter with its orifice at the bladder neck has been attempted with a dismal 14% success rate.[49] When the ectopic ureter is associated with the upper pole of a duplex renal unit, function of the upper pole is usually poor, and a partial nephroureterectomy is generally performed. Rarely, the upper pole functions enough, and a ureteropyelostomy or ureteroureterostomy to drain the ectopic system into the lower pole system is appropriate; however, if the lower pole pelvis is intrarenal and the lower pole ureter nondilated, this approach is technically less feasible. If the function of the ectopic ureter is worth saving, another option is reimplantation into the bladder, although the ureter is usually sufficiently dilated to warrant tailoring.

Management of the terminal ureteral stump in the case of an ectopic ureter is controversial. If an ectopic ureter enters into the introitus or vagina, the entire distal ureter usually need not be removed because the distal ureteral segment is a rare source of later problems.[135,156] If the distal segment becomes a source of stasis and infection, marsupialization of the ureter, usually a Gartner duct cyst, into the vagina corrects the problem. If nephroureterectomy without distal ureterectomy is performed in a urinary ectopic ureter ending in the bladder neck or urethra, reflux of voided urine into the residual ureteral stump is likely to occur. The ureteral stump may lead to a small amount of dribbling incontinence after micturition or, more commonly, recurrent urinary infection.

Plaire and colleagues[145] reported the need for additional surgery to remove the ureteral stump in 12% of patients with ectopic ureter previously treated with an upper tract approach. Removal of the ureteral stump is more likely to be needed for urinary ectopic ureters. Although the dissection behind the bladder can be tedious, if dissection is kept immediately on the wall of the ureter, there is no reason for the bladder neck or external sphincter to be damaged. The transtrigonal approach can be very useful. In a postpubertal girl, excision may be accomplished transvaginally. If the ectopic ureteral stump is not too large, its lining can be destroyed endoscopically using a Bugbee electrode to obliterate the ureteral lumen. Laparoscopic removal of distal ureteral stumps also has been described.[157]

Ectopic Ureter in Boys

Ectopic ureters in boys may end in the bladder neck, posterior urethra to the level of the verumontanum, or mesonephric duct derivatives: epididymis, seminal vesicle, or vas deferens. The most common site of termination is the posterior urethra in one half of male ectopic ureters (Fig. 26-16)[133]; one third join the seminal vesicle.[158,159] An ectopic ureter to the male genital tract may manifest as epididymitis. Any prepubertal boy with epididymitis requires evaluation for an ectopic ureter.[160] In some boys, symptoms caused by a genitally ectopic ureter do not manifest until the onset of sexual activity. At that time, a man may present with epididymitis, prostatitis, seminal vesiculitis, or occasionally an infected seminal vesicle cyst that may lead to pain with a bowel movement or tenderness on rectal examination.[161] Because ectopic ureters in boys enter above the external sphincter, they generally do not produce incontinence as in girls. Symptoms of flank pain and UTI are more common. A dilated single-system ectopic ureter into the prostatic urethra may elevate the bladder neck, causing outlet obstruction.[162]

A high index of suspicion is required to diagnose an ectopic ureter in a boy. An ectopic ureter entering the genital tract is often single and drains a nonfunctioning renal unit.[136,151,163] Ultrasonography may show a dilated ureter and its associated renal element. In the case of an ectopic ureter associated with a duplex renal unit, the indirect signs of hydroureteronephrosis of the upper pole unit (described previously) with respect to ureteroceles again apply. The greatest diagnostic difficulties arise in duplex renal units when there is a tiny upper pole unit draining into a minimally obstructed ectopic ureter with little dilation.[23]

Most ureters ectopic to the urethra or bladder neck reflux,[135] and careful examination of the oblique views from a VCUG and use of the cyclic voiding technique may enable the diagnosis to be made (see Fig. 26-16). In boys, as in girls, ectopic ureters at the level of the sphincters may show the paradoxical finding of obstruction and reflux. Occasionally, when the ectopic ureter is outside the urethra, the ejaculatory duct is so dilated as to permit reflux.[164] MRI may be useful for showing the ectopic ureteral anatomy.[165] The advent of fast-scan MRI technology should improve the utility of this diagnostic study in pediatric patients.

Cystoscopy and examination under anesthesia are useful in establishing the diagnosis of ectopic ureter. A mass may be palpated in the area of the seminal vesicle, or elevation of the bladder floor over a cyst ("pseudoureterocele") may be noted at cystoscopy. The ectopic ureteral orifice may be seen at the bladder neck or urethra, or there may be an enlarged ejaculatory duct that permits a retrograde study to establish the diagnosis. When there is single ureteral ectopy, a hemitrigone is present. Occasionally, a vasogram is useful in defining the anatomy.[132]

Treatment of an ectopic ureter associated with duplex units in boys usually involves removal of the associated poorly functioning renal unit. Rarely, function is adequate to justify a ureteropyelostomy or ureteroureterostomy. Because the ectopic ureter is usually dilated, reimplantation of the duplex ectopic ureter into the bladder is a less attractive alternative. These issues arise only rarely in boys because most duplex ectopic ureters occur in girls.

With a single-system ectopic ureter, a functioning renal unit worthy of salvage occurs more frequently with ectopy to the urinary tract.[135] In contrast, when the single ectopic ureter enters a mesonephric remnant, the kidney usually functions poorly, and a nephroureterectomy is appropriate. When an ectopic ureter enters the male genital duct, it may be unfit for the passage of sperm, and ligation of the vas may be required to avoid recurrent epididymitis.

Bilateral Single Ectopic Ureters

Bilateral single ectopic ureters are rare, and when present at the level of the urethra or more distally are usually associated with a poorly developed bladder with an absent trigone with a poorly developed bladder neck.[137,166-168] Very rarely, there is bladder agenesis.[169] Associated genital and anal anomalies are very common with bilateral single ectopic ureters, as are associated renal dysplasia or hydronephrosis.[153]

Girls most commonly are found to have bilateral single ectopic ureters located in the distal urethra. Infant girls usually present with UTI and continuous incontinence. Older girls most commonly present with incontinence. Girls generally have worse bladders and more severe renal anomalies than those seen in boys with bilateral single ectopic ureters.[166,167] Because some urine enters the bladder in boys, it is often of slightly larger capacity than the bladder seen in girls. Although enough urine may enter the bladder in boys to permit some voiding to occur, boys may also present with incontinence.

When bilateral single ectopic ureters are present at the bladder neck level, children may present with infection and upper urinary tract dilation from obstruction or reflux or both, but the bladder neck is generally better formed, and continence is more likely. When one ureter is ectopic to the urethra and one is ectopic at the bladder neck, there is an intermediate condition, but incontinence is usually present.[137]

Diagnosis of bilateral single ectopic ureters is usually established by a carefully executed IVP and VCUG.[170,171] The associated renal units may show very poor function. The VCUG shows a small bladder with an open bladder neck. If the ectopic ureters are in the urethra, reflux is commonly present, and the VCUG usually makes the diagnosis. If the ureters are further down the ectopic pathway than the urethra, they usually are not shown by the VCUG. Ultrasound or MRI may be useful. A retrograde flush vaginogram with a Foley balloon occluding the introitus may similarly detect refluxing vaginally ectopic ureters. At cystoscopy, a child with bilateral single ectopic ureters usually is noted to have a poorly defined, funnel-shaped bladder neck and a small bladder capacity. In boys, the ureteral orifices are usually located in the distal bladder neck or urethra, but in girls, they may be more ectopic and more difficult to locate.

A child who is incontinent with bilateral single ectopic ureters presents a major challenge to reconstructive surgery. In the case in which bladder capacity seems to be adequate, reimplantation of the ureters into the bladder and a Young-Dees-Leadbetter type of reconstruction of the bladder outlet may be appropriate.[172] If bladder capacity is inadequate, it may be feasible to turn the entire bladder into a long detrusor tube to provide continence and to create an adequate reservoir by augmentation cystoplasty with antirefluxing anastomoses of the ureters to the bowel segment.[173] The difficulty of creating a continent bladder outlet in this patient population frequently leads to eventual bladder neck closure and appendicovesicostomy to achieve continence.[174]

REFERENCES

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PART IV

BLADDER

CHAPTER 27

PATHOPHYSIOLOGY OF BLADDER DYSFUNCTION

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During the first few years of life, the bladder develops and matures into a unique organ that is capable of storing urine to be emptied in socially appropriate situations. During the filling phase, quiescence and relaxation of the detrusor smooth muscle facilitates the unfolding and stretching of the bladder wall in a viscoelastic manner, allowing urine to be stored at low pressure. Involuntary urine leakage is prevented by contraction of the striated external urinary sphincter muscle. During the voiding phase, the detrusor muscle contracts as a unit to increase the intravesical pressure, and the sphincter muscles relax, decreasing outflow resistance, allowing complete bladder emptying.[1-4] From early infancy, there is a gradual development to an adult type of voluntary micturition control that conforms to the social norms; this control depends on an intact nervous system in addition to at least three other events occurring concomitantly: (1) an increase in functional storage capacity, (2) maturation of function of the external urinary sphincter, and (3) achievement of volitional control over the bladder-sphincter unit so that the child can voluntarily initiate or inhibit a micturition reflex.[4-7]

The dynamics and functional disturbances of the lower urinary tract in children are very different from those in adults and are often associated with no identifiable anatomic abnormalities. Also, continuous changes and evolution in normal bladder-sphincter function occur as growth and maturation take place.[8-11] Various functional derangements of the bladder-sphincter-perineal complex may occur during this sophisticated course of early development of normal micturition control mechanisms. Infant boys normally void with significantly higher detrusor pressures than infant girls and adults.[8] This physiologic detrusor hypercontractility tends to diminish and normalize after the second year of life. What should be regarded as normal detrusor pressures in a boy a few months old can be abnormally high for a girl of similar age or an older boy. One type of bladder dysfunction often may progress with time and evolve imperceptibly into another, without a sharp distinction between the different stages, and these acquired functional disorders may overlap with other types of bladder functional disturbances, which may have a more organic but congenital underlying pathophysiologic basis.

Bladder-sphincter dysfunction, often manifested as urinary incontinence, is a common condition in childhood. In a group of 1192 otherwise healthy American children, daytime urinary incontinence was noted in 10%, with a higher prevalence among girls.[12] In another survey of 3556 7-year-old Swedish schoolchildren, the incidence of daytime incontinence was 6% in girls and 3.8% in boys.[13] In addition, the symptom of urgency is recognized by 35% of children 7 to 10 years old.[14] Different types of bladder dysfunction occur widely and often play a significant role in the pathophysiology of various urologic disorders in childhood, such as primary vesicoureteral reflux (VUR) and primary nocturnal enuresis, and are often associated with various urodynamic abnormalities that may act as the initiating and the perpetuating factors for the presenting conditions.[15-20] Successful treatment of the underlying bladder dysfunctions can lead to spontaneous resolution of reflux and incontinence, and prevent further recurrence of urinary tract infection (UTI). Advances in urodynamic techniques specially designed for infants and young children have allowed more accurate assessment of these functional disorders and provided much better understanding of the pathophysiology and scientific basis for their therapy.[21-24]

ANATOMY AND INNERVATION OF THE BLADDER

Anatomy

Extensive postmortem studies since the 1980s have substantially improved our understanding of the functional anatomy of the lower urinary tract.[2,25-28] The reservoir function is determined by concomitant activity of the detrusor muscle and the bladder outlet (consisting of the bladder neck, proximal urethra, and striated muscle of the pelvic floor).[2] The bladder wall consists of three layers: mucosa, detrusor muscle, and adventitia. The detrusor represents a meshwork of smooth muscle bundles arranged to make it possible to act as a single functional unit. The detrusor smooth muscle fiber is characterized by its ability to elicit nearly maximal active tension over a wide range of length, which makes the bladder compliant and allows urine filling from the upper tract at low pressures.[3]

It is generally accepted that the sphincter plays an important role in maintaining urinary continence by closure of the bladder neck and proximal urethra. The external urinary sphincter in the fetus [29] and in adults is a cylindrical structure, accentuated anteriorly and thinned out or even absent posteriorly, giving a characteristic horseshoe or omega shape on cross section. It consists of an inner layer of smooth muscle and an outer layer of striated muscle, extending from the apex of the prostate to invest the length of the membranous urethra in males. In females, the striated sphincter is less well developed and extends from the bladder neck to the midurethra.

Immature detrusor-sphincter coordination with some degree of detrusor overactivity and interrupted voiding commonly occurs in the first 1 to 2 years of life.[16,30] This may be

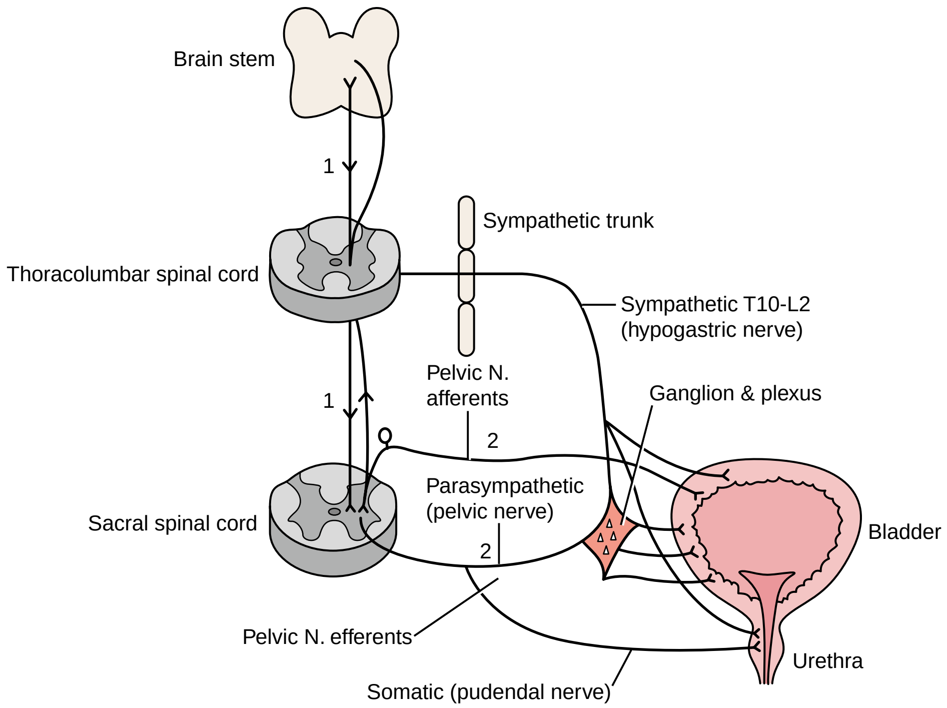


Figure 27-1 Innervation of the bladder-sphincter complex.

due in part to the development of the sphincter in a concentric pattern as a closed ring at around 20 weeks of gestation,[31] which fused posteriorly to form a tail-like structure that was directed toward the perineal body. Posterior splitting of the striated sphincter, starting caudally and progressing in a cephalad manner, then occurred during the first year of life, coinciding with gradual resorption of the "tail," to give way eventually to a mature omega-shaped structure.[31] Although radiographic and urethral pressure measurement studies have indicated the existence of a physiologic internal sphincter, a clear anatomic internal sphincter between the bladder and the urethra has not been well delineated. At micturition, the bladder base, bladder neck, and proximal urethra contract simultaneously as a unit, producing a funneling effect that opens the bladder outlet and initiates voiding.

Innervation

Activation, coordination, and integration of various parts of the bladder-sphincter complex involve the central somatic and the autonomic nervous systems through three sets of peripheral nerves: sacral parasympathetic (pelvic nerve), thoracolumbar sympathetic (hypogastric nerves and sympathetic chain), and sacral somatic (primarily the pudendal nerve) nerves (Fig. 27-1).[2,3] Parasympathetic nerve fibers run in the pelvic nerve (from S2 to S4) to supply the pelvic and vesical plexuses before entering the bladder. Parasympathetic ganglia are found in these plexuses and in the bladder wall. Sympathetic nerves arise from segments T10 to L2 of the spinal cord and go to the inferior mesenteric ganglion through the sympathetic trunk. From the inferior mesenteric ganglion, the nerve fibers pass to the pelvic plexus and bladder through the hypogastric nerves. There is also sympathetic innervation originating from T10 to L2 supplying the detrusor and urethral sphincter.[32] The somatic nervous system (pudendal nerve) supplies the periurethral pelvic floor musculature.[3] All three nerves (hypogastric, pelvic, and pudendal) carry motor and sensory neurons.[33] The sensory and motor innervation to the bladder and the urethral sphincter originate from parasympathetic ganglia located in the second, third, and fourth segments of the sacral spinal cord.[32] Within the spinal cord, information from bladder afferents is integrated with information from other visceral and somatic sources and projected to the brain stem centers that coordinate the micturition cycle.[33]

DEVELOPMENT OF NORMAL BLADDER FUNCTION AND MICTURITION CONTROL

During the first 2 to 3 years of life, there is progressive development from an initially indiscriminate infantile voiding pattern to a more socially conscious and voluntary, or adult, type of micturition. Through an active learning and cognitive process, a child acquires the ability to inhibit and delay voiding voluntarily if this is socially inconvenient, and initiate and allow voiding to proceed when it becomes socially convenient.

Voiding Frequency

During the last trimester, the voiding frequency of the fetus is approximately 30 times every 24 hours.[6] In the first few days of life, voiding is usually very infrequent. Voiding frequency increases rapidly after the first week, peaks at the age of 2 to 4 weeks (an average of once per hour), and then decreases and subsequently stabilizes after 6 months to about 10 to 15 times a day toward the end of the first year of life.[6,11,34-37] During the next 2 to 3 years, the voiding frequency decreases further to about 8 to 10 voids a day, and the mean voided volume increases by threefold to fourfold.[6,11] This reduction in voiding frequency observed during the first few years of life seems to be related mainly to an increase in bladder capacity in parallel to body growth, which is proportionately greater than the simultaneous increase in urine volume production.[4,5,35] By age 12 years, the voiding pattern is very similar to that in an adult and usually comprises four to six voids a day.

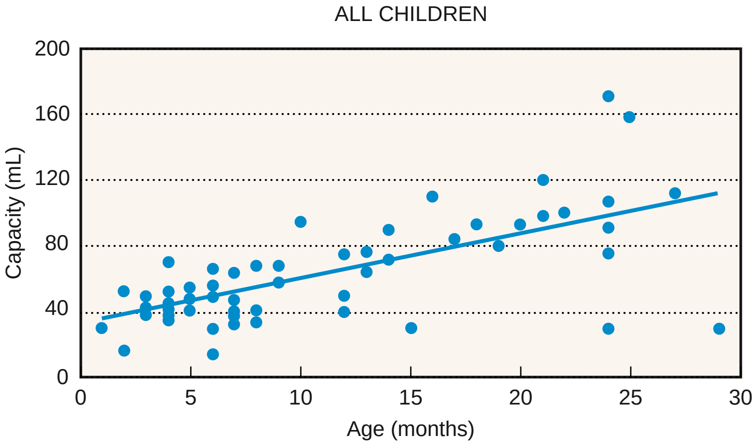


Figure 27-2 Progressive increase in bladder capacity with age that can be expressed by the formula: Capacity (mL) = 30 + 2.7 × age (mo). (Courtesy of CK Yeung and colleagues, unpublished data.)

Bladder Volume, Voided Volume, and Emptying Efficiency

As a child grows, the bladder volume increases progressively to provide adequate reservoir function for urine storage; this is crucial in the development of normal bladder function and urinary continence. Studies by various workers have indicated that the expected bladder capacity at a certain age can be accurately estimated and expressed as a function of age. There are no significant differences between boys and girls. For young infants, the bladder capacity increases with age according to the following formula[34,38]:

Bladder volume (mL) = 38 + [2.5 × age (mo)]

For children after the first 1 to 2 years of life, the expected bladder capacity for age can be accurately estimated and expressed by[21,39]:

Bladder volume (mL) = 30 + [age (yr) × 30]

Other workers have derived similar formulas for calculating bladder capacity relative to age (Fig. 27-2).[40,41] The suggested minimal bladder capacity in milliliters expected for age = (16 × age) + 70.[42]

Throughout infancy and early childhood, the mean voided volume of each micturition increases in parallel with the increase in bladder volume. A significant proportion of infants up to 12 months old exhibit an interrupted and uncoordinated form of micturition as a result of incomplete maturation of detrusor-sphincter coordination.[8,16,34,43,44] The urine flow is interrupted and occasionally may be brought to a complete stop for 1 to 2 minutes before restarting, producing a few small and interrupted voids in quick succession. Despite this interrupted pattern, the overall bladder emptying efficiency, calculated as the ratio of voided volume to capacity (voided volume + residual volume), is usually greater than 80% after the voiding, or quick succession of small voids, is completed.[8,11,16,34,45]

Detrusor Pressure at Voiding

The detrusor pressure during micturition in healthy infants has always been poorly understood because of (1) technical difficulties in performing urodynamic studies in young infants and (2) ethical considerations and a lack of justification for doing such studies. High voiding pressures have been recorded in healthy asymptomatic infant siblings of children with VUR,[8] especially in infant boys (mean maximal detrusor pressure with micturition [P_{det}max] 127 cm H_2O; range 84 to 211 cm H_2O). Similar pressures were found during natural fill cystometry in infants with normal lower urinary tracts (as indicated by a normal micturating cystourethrogram) with documented significantly higher P_{det}max than in adults (Yeung and colleagues[8]). Infant boys voided with significantly higher pressures than infant girls (meanP_{det}max of 118 cm H_2O versus 75 cm H_2O, $P < .03$).[8,16,45] These pressures have been shown to be maximum during the first year of life and then to decrease progressively with age (Fig. 27-3).

In about half of the infants studied by Yeung and colleagues,[8] the elevated detrusor pressures during micturition exhibited varied degrees of fluctuating peaks and troughs, associated with an interrupted or "staccato" type of urinary stream. With each abrupt cessation of urinary flow, there was a simultaneous sharp increase in detrusor pressure, strongly suggesting detrusor-sphincter incoordination. The urinary stream resumed in conjunction with a sharp decrease in the detrusor pressure (Fig. 27-4A). Occasionally, the urine flow might stop completely for 1 to 2 minutes or even more before restarting, producing a few small and interrupted voids in quick succession.[8,16,45] Despite this interrupted pattern, the overall bladder emptying efficiency, calculated as the ratio of voided volume to capacity (voided volume + residual volume), is usually greater than 80% after the voiding, or quick succession of small voids, is completed.[8,11,16,34,45] These interrupted or staccato voids, observed in 20% to 70% of infants with normal lower urinary tracts in different series, tended to disappear with increasing age and were thought to represent variations between individual infants in the maturation of detrusor and sphincter coordination during the first 1 to 2 years of life.[8,16,34,43,44]

Using videocystometry with fluoroscopic control combined with natural fill urodynamics in conjunction with perineal electromyography studies in infants with a history of UTIs, the high detrusor pressures during micturition and interrupted voids in infancy were shown to be due to detrusor-sphincter incoordination.[8,45] Periods of increase in perineal or sphincter electromyographic activities appearing during the voiding phase were associated with a sudden cessation of urinary flow in conjunction with a simultaneous isometric increase or high peak of detrusor pressure.

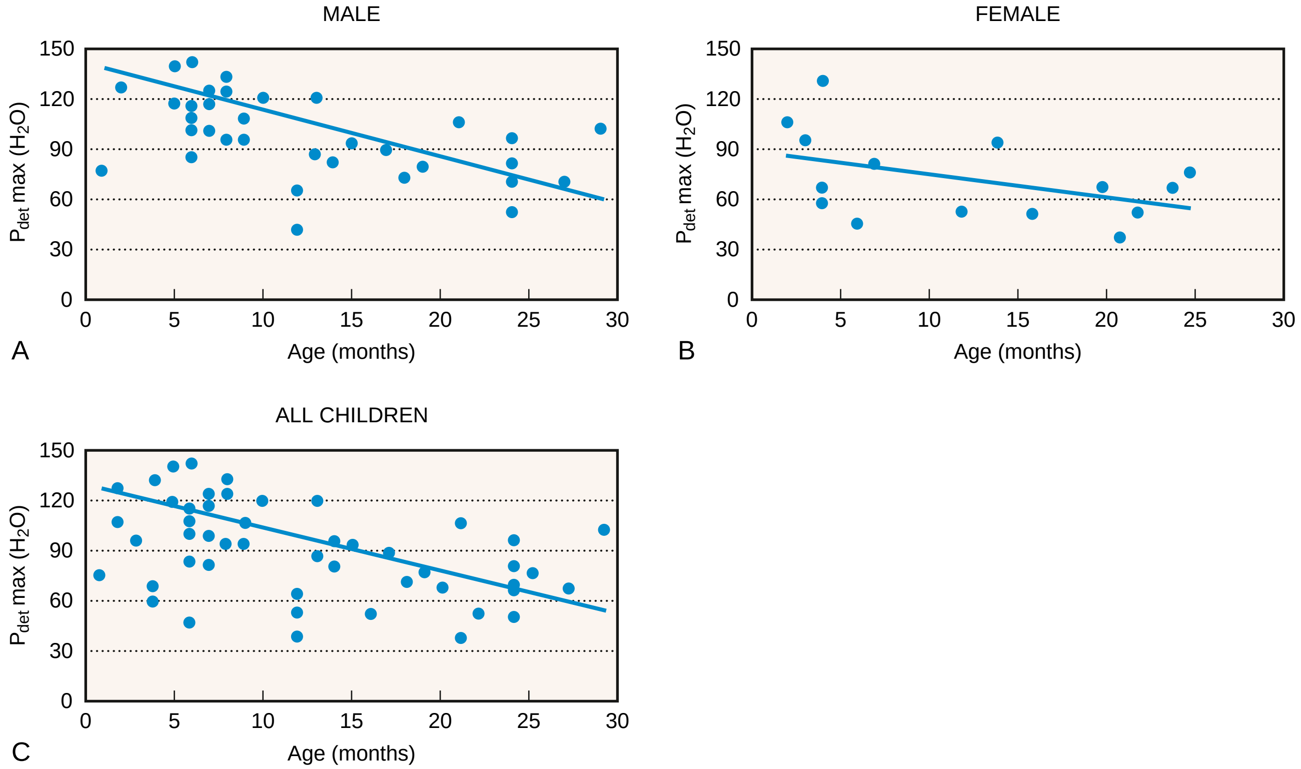


Figure 27-3 **A-C,** Progressive decrease in maximal detrusor pressure during micturition (P_{det} max) with age in infants and young children with normal lower urinary tracts using natural filling cystometry in boys **(A),** in girls **(B),** and in all children **(C).**

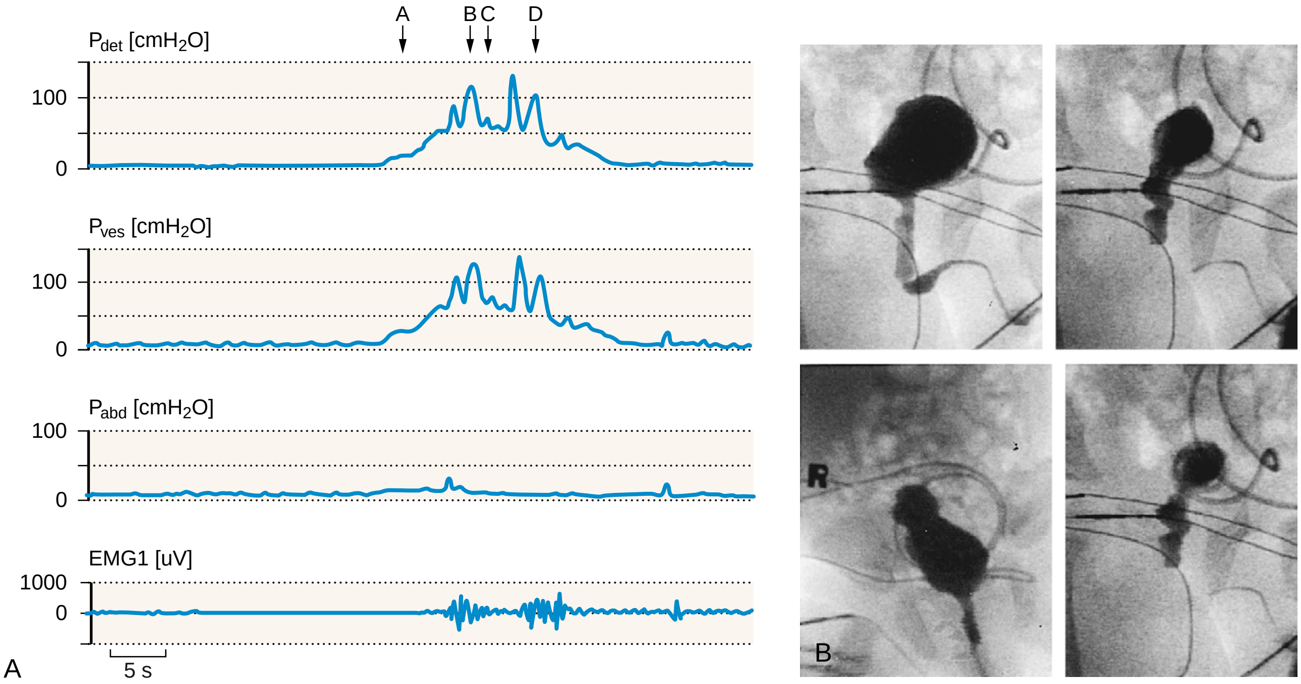


Figure 27-4 Interrupted voiding pattern caused by detrusor-sphincter dyscoordination as revealed by urodynamic study with simultaneous perineal electromyographic (EMG) monitoring and videocystourethrography. **A,** *Arrows* in *top* figure correspond to urethrograms at *bottom.* **B,** Urinary flow starts. Premature sphincter contraction and urethral closure as evidenced by the urethrogram and increase in sphincter EMG activities lead to a sharp spike of detrusor pressure (isometric increase) associated with a paradoxical abrupt cessation of urinary flow. Urinary flow resumes in parallel with sphincter relaxation. Repeated sphincter contraction leads to another sharp increase in detrusor pressure and paradoxical interruption of urinary flow. P_{abd}, abdominal pressure; P_{det}, detrusor pressure; P_{ves}, intravesical pressure.

In contrast, resumption of urinary flow was associated with relaxation of the external urinary sphincter and a paradoxical decrease in detrusor pressure (Fig. 27-4B). The detrusor pressure associated with the initiation of urinary flow was usually significantly lower than the maximal detrusor pressure during micturition (P_{det}max). The latter was mostly associated with detrusor-sphincter incoordination and interruption of flow, and was considerably higher than the maximal detrusor pressures usually encountered in adults.

Evolution of Normal Micturition Control

In full-term fetuses and newborns, micturition is modulated by higher centers, and previous theories that voiding in this age period is spontaneous and mediated by a simple spinal reflex are probably an oversimplification. Ohel and colleagues[46] reported that fetal micturition is a behavioral state–dependent event. Intrauterine micturition is not randomly distributed over various behavioral (sleep and arousal) states, and occurs almost exclusively while the fetus is awake. It has been observed that micturition in a term fetus can be elicited by vibroacoustic stimulation, indicating that the micturition reflex is probably under higher neural center control and already quite well developed at near-term gestational stages.[47] Healthy preterm neonates micturate more often during sleep than when awake and with more interrupted voids than their post-term counterparts, whose bladder is normally quiescent and stable.[8,44]

This inhibition (or lack of facilitation) of detrusor contractions during sleep also is observed in infants and children with neurogenic bladder who have marked detrusor overactivity during wakeful periods. In response to bladder distention during sleep, an infant nearly always exhibits clear electroencephalographic evidences of cortical arousal, facial grimaces or limb movements, or actual awakening.[8,16,45] Sleeping infants are always seen to wake up before bladder activity returns and voiding occurs. The arousal period may often be transient, however, and the infant may cry and move for a brief period before micturition and then shortly afterward go back to sleep again. Because this wakening response to bladder distention is already well established in human newborns, it follows that the control of micturition, even in early infancy, probably involves more complicated neural pathways and higher centers than has hitherto been appreciated. Animal studies show that postnatal development of bladder control in mammals is associated with a sophisticated integration of central and peripheral neural pathways that already exist at birth and is not mediated by simple spinal reflexes alone.[48,49] There is also strong evidence suggesting that a pronounced reorganization of such preexisting synaptic connections and neural pathways involved in bladder control occurs during the early postnatal period.

Extensive studies by De Groat and others[50-54] using experimental animals have indicated that early postnatal maturation of bladder function probably occurs at different levels: (1) changes in the properties of detrusor muscle, (2) developmental modifications in the peripheral innervation of the bladder, and (3) alterations in central synaptic circuitry and neuroplasticity in the parasympathetic reflex pathways to the bladder. Recordings of spontaneous activities in bladder smooth muscle in neonatal rats showed much larger amplitude and more synchronous rhythmic contractions compared with those observed in adult rats.[55] This evidence suggests that there is a progressive reduction in intercellular communication between detrusor smooth muscle cells, resulting in less spontaneous activity and more efficient urine storage during early postnatal development.

In addition, peripheral and central neural mechanisms change extensively during the early postnatal period. In cats (and some other species), micturition during the newborn period depends on an exteroceptive somatovesical reflex triggered when the mother licks the perineum of the kittens.[50-52] This somatovesical reflex, processed in the sacral spinal cord, disappears in older animals, but may reappear after spinal cord injury. Further neuroanatomic studies have indicated that spinal bladder reflexes are mediated via interneurons located immediately adjacent to, and synapsing with, the sacral preganglionic neurons.[53] This interneuron–preganglionic neuron synaptic transmission is very efficient immediately after birth, but is very abruptly downregulated during the third postnatal week when the mature supraspinal micturition reflexes start to appear.[52] Transection of the spinal cord prevents this downregulation, indicating that the higher neural centers play an important role in this synaptic remodeling, which contributes to postnatal development of micturition reflexes.

During the second or third year of life, there is progressive development toward a socially conscious continence, and a more voluntary, or adult, type of micturition control emerges. The child becomes more aware of the sensation of bladder distention and the urge to urinate, and social norms and embarrassment associated with urinary incontinence. Through an active learning process (which includes toilet training), the child acquires the ability to inhibit and delay voiding voluntarily until a socially convenient time, then actively initiate urination even when the bladder is not very full, and allow urination to proceed to completion. Besides an intact neural pathway and awareness of social norms, this natural evolution of micturition control mechanisms depends on multiple factors, including the gradual increase in functional bladder capacity, maturation of detrusor-sphincter coordination, and progressive development of voluntary control over the whole bladder-sphincter-perineal complex. The final steps are usually achieved at age 3 to 4 years, when most children have developed the adult pattern of urinary control and are dry day and night.

Neurologic control of normal micturition occurs at different levels of the central nervous system, from the spinal cord with the *sacral micturition center* to the brain stem with the *pontine micturition center,* the cerebellum, basal ganglia, limbic system, thalamus and hypothalamus, and cerebral cortex.[2,56-58] The bladder is unique among other visceral organs in that its function is under the control of the somatic and the autonomic nervous systems. Besides acetylcholine and norepinephrine, various other neurotransmitters, including prostaglandin substance P, opioid peptides, vasoactive intestinal peptide, and neuropeptide Y, are involved during bladder stimulation.[57] Simple manipulation of adrenergic and cholinergic receptors may only partially abolish the effect of neural stimulation, which explains why pharmacologic blockage of the classic neurotransmitters (acetylcholine and norepinephrine) alone may fail to elicit the expected full clinical response.

CLASSIFICATION OF BLADDER DYSFUNCTION

Many definitions of bladder dysfunction that are adequate in adults are irrelevant in children and vice versa. Advances in research on incontinence and enuresis in childhood have required clarification and modification of the terminology. Various classifications for bladder dysfunctions in children have been described since the 1970s.[59-61] To avoid confusion, the International Children's Continence Society (ICCS) proposed a classification in 1997, with a standardized set of terminology. This has been revised more recently,[62] and the Standardisation

Table 27-1 Terms Defined in the International Children's Continence Society Terminology (2006)*

Bladder diary	Standard chart to be completed by the child or family, used for evaluation of bladder function and including data regarding at least voided volumes, voiding frequency, fluid intake, nocturia, enuresis, and incontinence episodes
Daytime voiding frequency, decreased	≤3 voids per day
Daytime voiding frequency, increased	≥8 voids per day
Detrusor overactivity	Observation during cystometry of involuntary detrusor contractions during the filling phase; this replaces the term *detrusor instability*
Detrusor-sphincter dyssynergia	Cystometric observation of a detrusor voiding contraction concurrent with an involuntary contraction of the urethra
Detrusor underactivity	Cystometric observation of a contraction of decreased strength or duration or both, resulting in prolonged bladder emptying or a failure to achieve complete bladder emptying
Dysfunctional voiding	Habitual contraction of the urethral sphincter during voiding, as observed by uroflow measurements
Enuresis	Intermittent incontinence of urine while sleeping, synonymous with (intermittent) nocturnal incontinence; the term is used regardless of whether daytime incontinence or other lower urinary tract symptoms are also present; nocturnal may be added for extra clarity
Enuresis, monosymptomatic	Enuresis in a child without any (other) lower urinary tract symptoms
Enuresis, nonmonosymptomatic	Enuresis in a child with (other) lower urinary tract symptoms, such as daytime incontinence, urgency, or holding maneuvers
Enuresis, primary	Enuresis in a child who has previously been dry for <6 mo
Enuresis, secondary	Enuresis in a child who has previously been dry for ≥6 mo
Expected bladder capacity	Age-related expected maximum voided volume, as calculated via the formula [30 + (age in years × 30)] in mL, and used as a standard for comparisons
Frequency-volume chart	Chart to be completed by the child or family used for evaluation of bladder function, but not including all data required of a bladder diary; see above
Incontinence, continuous	Continuous leakage of urine, not in discrete portions, which indicates malformation or iatrogenic damage
Incontinence, intermittent	Leakage of urine in discrete portions during the day or night or both
Incontinence, nocturnal	See *enuresis*
Overactive bladder	Condition affecting patients experiencing urgency symptoms; it replaces the term *bladder instability*
Polyuria, nocturnal	Nocturnal urine output >130% of expected bladder capacity; see above
Residual urine	Urine left in the bladder after voiding; residual urine >5-20 mL indicates incomplete bladder emptying
Underactive bladder	Condition affecting patients with low voiding frequency and the need to increase intra-abdominal pressure to void; it replaces the term *lazy bladder*
Urge incontinence	Incontinence in patients experiencing urgency (i.e., incontinence in children with overactive bladder)
Voided volume	Voided volume at micturition, as documented in a bladder diary; it replaces the term *bladder capacity*
Voided volume, maximum	Largest voided volume, as documented in a bladder diary; it replaces the term *functional bladder capacity*
Voiding postponement	Incontinence in the presence of habitual holding maneuvers

*This table is provided as a quick reference for terms used in association with children who are investigated for lower urinary tract malfunction.

Adapted from Nevéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. *J Urol.* 2006;176:314.

Committee of the ICCS has published the new recommendations for a terminology for lower urinary tract function and malfunction, and the present chapter has tried to follow these new recommendations (Table 27-1).

Certain general principles for the "new" terminology[62] have been used, and most importantly it has been considered that the terms to be used should be descriptive and with a focus on the child as a growing, maturing individual. When possible and reasonable, pediatric terminology should follow the terminology for adults as established by the International Continence Society.[33] The new terminology provides guidelines for the terminology of lower urinary tract function and malfunction in children. The purpose is to use the same terminology in children with neuropathic and non-neuropathic bladder dysfunction.

The old term *detrusor instability* is replaced by *detrusor overactivity*, and *unstable bladder* has been replaced by *overactive bladder*. The distended, weakly contracting *lazy bladder* with residual urine is now called *detrusor underactivity*, and the presence of sphincter contractions during the voiding phase (earlier called *detrusor-sphincter dyscoordination*) is known as *dysfunctional voiding*. *Incontinence* is any involuntary loss

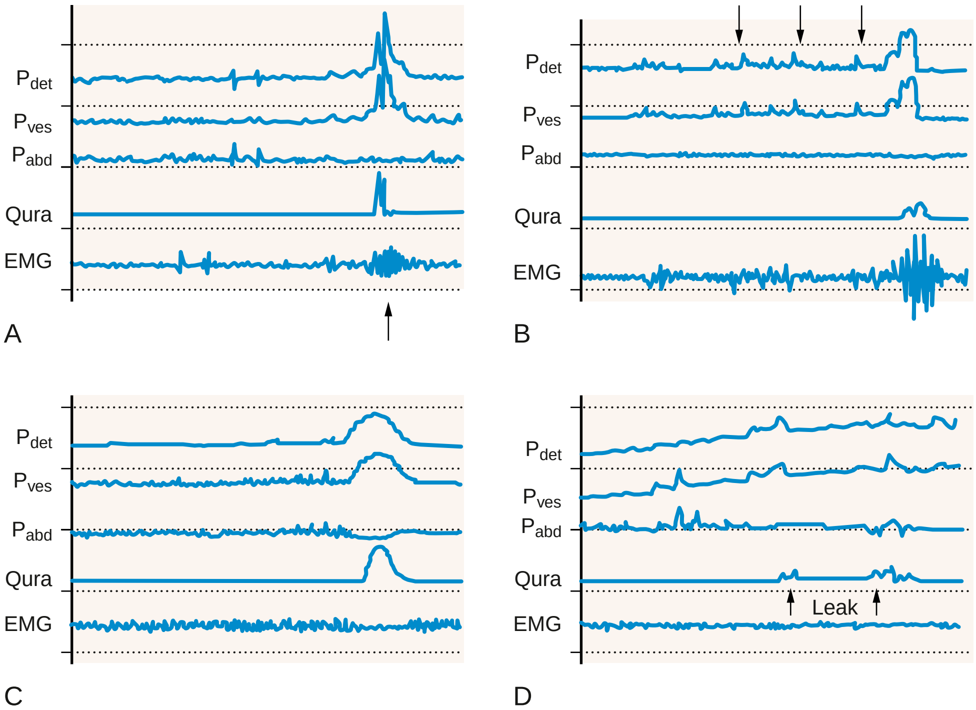


Figure 27-5 Various bladder functional patterns. **A,** Dyssynergic pattern with an increase in sphincter electromyogram (EMG) activities during micturition *(arrow),* leading to an interrupted urinary flow. **B,** Overactive bladder, characterized by frequent unstable detrusor contractions *(arrows)* during the filling phase. **C,** Normal female micturition pattern; note the pelvic floor relaxation as evidenced by a decrease in abdominal pressure during micturition. **D,** Bladder with low (poor) compliance as evidenced by a rapid increase in intravesical pressure during filling, often associated with urinary leakage *(arrows).* P_{abd}, abdominal pressure; P_{det}, detrusor pressure; P_{ves}, intravesical pressure; Qura, uroflow.

of urine at a socially unacceptable time and place in a child past the age of bladder control. *Enuresis* means wetting while asleep, regardless of underlying cause. *Urgency* is best described as the sudden, urgent need to void, and is the hallmark of uninhibited detrusor contractions. When combined with incontinence and an increased voiding frequency (more than seven times per day), the syndrome is called *overactive bladder* or *urge incontinence*.

The symptoms of lower urinary tract malfunction are classified according to their relationship to the voiding or storage facet of bladder function. Duration of symptoms is irrelevant to the use of these terms. Incontinence is called incontinence even if it occurs just once. Functional classification of bladder dysfunction is based on the functional state of the bladder-sphincter complex with respect to detrusor activity, bladder sensation, bladder compliance and capacity, and urethral function during the filling and the voiding phases of cystometry (Fig. 27-5).[23]

Non-neuropathic Bladder Dysfunction

One must be very cautious in assessing young children with apparent voiding dysfunctions because most of these dysfunctions are transitory or intermittent and do not persist after a period of successful toilet training. It has even been postulated that in making the transition from an infantile to an adult pattern of micturition control, all children may transiently display some degree of abnormal bladder-sphincter function.[5] If voiding dysfunctions are persistent well beyond the period of toilet training, especially if associated with urinary complications such as recurrent urosepsis, the possibility of underlying anatomic and neurologic causes must be considered and duly evaluated.

The various conditions described under the category of non-neuropathic bladder-sphincter dysfunction, including overactive bladder, dysfunctional voiding, fractionated voiding, and underactive bladder, should not be viewed rigidly as separate and distinct entities because one may represent a transitional phase of a complex sequence of events. A girl with dysfunctional voiding may start with having detrusor overactivity associated with sphincter and pelvic floor overactivity, then gradually develop fractionated voiding with increasing postmicturition residues, and finally develop bladder decompensation and an underactive bladder (previously *lazy bladder syndrome*).[63]

Use of the term *non-neuropathic* is based purely on the fact that no obvious and identifiable neurologic lesion can be identified. Conditions such as the urofacial syndrome complex (Ochoa syndrome) and Hinman syndrome behave almost identically to the typical neuropathic bladder-sphincter dysfunctions. It is conceivable that they do have an organic underlying neurologic cause, although the exact neuroanatomic lesion has not yet been identified. The distinction between neuropathic and non-neuropathic bladder dysfunctions may be unclear. The terms to be used are noted in Table 27-1.

Bladder-Sphincter Dysfunction during Bladder Filling

Overactive Bladder (Previously Unstable Bladder), Voiding Postponement, and Urge Incontinence

The subjective hallmark of the overactive bladder is urgency, with incontinence and voiding frequency also often present. The syndrome is characterized by frequent attacks of sudden and imperative sensations of urge, often countered by voluntary hold maneuvers, such as squatting in girls (the Vincent curtsy sign).[64,65] Urgency is typically found in girls and is caused by detrusor overactivity during the filling phase, causing the burning sensation or urge to void even at a small bladder volumes. In voiding postponement, the detrusor contractions are often counteracted by voluntary contraction of the pelvic floor muscles by the girl in an attempt to compress the urethra externally (hold maneuvers). Despite the hold maneuvers, the child still has frequent urine leakage, manifested as damp patches.

Urge incontinence usually consists of small quantities of urine loss and occurs most often in the afternoon, or when the child is preoccupied in play or other activities and is not alert enough to contract the pelvic floor in response to the urge sensation. Children with urgency have small voided volumes for age and often choose to drink extremely little to escape the social embarrassment of the urine incontinence and frequent imperative urges to go to the toilet. Micturition is usually in small quantities, but is otherwise unremarkable, with complete relaxation of the pelvic floor musculature in most instances. The signs and symptoms in patients with detrusor overactivity may vary and depend on the frequency and forcefulness of the contractions and on the effectiveness of the hold maneuvers by voluntary pelvic floor contraction. In addition, habitual voluntary pelvic floor contraction to counteract every urge to void may often lead to inappropriate postponement of defecation, constipation, and fecal soiling.[65,66] This condition should not be confused with encopresis in children with behavioral problems.

Urodynamic studies in children with overactive bladders usually reveal detrusor overactivity associated with a small cystometric bladder volume, but occasionally may be normal with incontinence only barely perceptible, particularly if conventional cystometry with artificial bladder filling rather than natural filling cystometry is used.[41] Artificial filling during cystometry may inhibit the detrusor response and attenuate its maximal contractile potential, rendering detrusor instability much less pronounced and undetectable.[41,67-69] The combined use of artificial filling cystometry and natural filling urodynamic studies is often helpful in such circumstances to delineate accurately the underlying bladder dysfunction.

Urinary Incontinence

Urinary incontinence can be defined as the involuntary loss of urine, owing to a failure of control of the bladder-sphincter unit, that is frequent enough to constitute a social or hygienic problem, and occurs in the absence of underlying anatomic causes.[23] Apart from urge incontinence that is associated with detrusor overactivity and urge syndrome as described earlier, other forms of functional urinary incontinence exist as a result of failure of the bladder storage or sphincter control mechanisms, or both. *Stress incontinence* represents the involuntary leakage of urine occurring at times when the intravesical pressure exceeds the bladder outlet or urethral resistance, in the absence of measurable detrusor contraction. In contrast to the situation in adults and particularly in elderly women, true stress incontinence is rare in children and is generally not associated with any demonstrable urodynamic abnormalities. It is likely that this condition may represent a mild form of bladder overactivity, with small unstable detrusor contractions appearing only on provocation or at times of increased intra-abdominal pressure. Insufficient bladder outlet or urethral resistance is usually not a main factor. Because the amount of urine leakage in most patients is usually small, the incontinence may sometimes be only scarcely discernible. It is possible that the actual incidence of this condition may be underestimated.

Giggle incontinence is usually seen in girls and is characterized by involuntary and typically unpredictable wetting during giggling or laughter. In contrast to stress incontinence, it produces a much larger volume of urine leakage, often amounting to complete bladder emptying. As in stress incontinence, however, cystometry may be completely normal or occasionally show some detrusor overactivity. Treatment is notoriously difficult, but sometimes a course of anticholinergic drugs may help to ameliorate the symptoms.

Bladder-Sphincter Dysfunction during Bladder Emptying

Dysfunctional Voiding

Dysfunctional voiding is characterized by incomplete relaxation or overactivity of the pelvic floor muscles during micturition, and the term may be applied only in the presence of staccato voiding on repeat uroflowmetry measurements or during urodynamic investigations. The term *dysfunctional voiding* merely defines dysfunction during voiding, and says nothing about the storage function of the bladder. In *staccato voiding*, the urinary stream is often delayed after the onset of detrusor contraction and is typically interrupted, resulting in a few small squirts of urine passed in quick succession. The interrupted voiding is caused by periodic bursts of pelvic floor muscle activities during micturition, resulting in the characteristic abrupt elevation or spikes of voiding pressures, coinciding with paradoxical cessation of urinary flow. The flow time is usually prolonged, and bladder emptying is often incomplete, resulting in increased postmicturition residues and a predisposition to UTIs.

Fractionated voiding is characterized by infrequent and incomplete emptying secondary to detrusor inactivity. Micturition occurs in several small and discontinued fractions because of poor and unsustained detrusor contractions, leaving significant postvoid residuals. Abdominal straining is usually evident as an effort to improve the bladder emptying. This straining is often paradoxically counteracted, however, by a reflex increase in activities of the pelvic floor muscles that is triggered by an increase in intravesical pressure. The bladder volume is usually large for age and may gradually increase as the condition progresses further, and overflow incontinence may ultimately develop.

The underactive bladder (previously *lazy bladder syndrome*) is generally regarded as the end point of longstanding dysfunctional voiding culminating finally in a fully decompensated system. As a result of the chronic functional bladder outflow obstruction, there is a gradual deterioration in detrusor contractility and emptying efficiency. The postmicturition residue and bladder capacity progressively increase, eventually developing into a large, floppy bladder with very inefficient emptying. The child uses abdominal straining as the main driving force for bladder emptying, and because an urge sensation is either absent or diminished, voiding is very infrequent, and occasionally the child may not void for 8 to 10 hours or even longer while at school or during other activities. The presenting symptom is often recurrent UTIs secondary to large postmicturition residues, and may be associated with overflow incontinence, constipation, or fecal soiling. Urodynamic studies typically reveal a large-capacity bladder with very high compliance on filling. Detrusor contractions are noticeably absent, and “voiding” is achieved mainly by abdominal pressures, resulting in a very fractionated flow pattern. Electromyography often shows increased activities of pelvic floor muscles with each abdominal strain.

Relationship between Bladder Dysfunctions, Vesicoureteral Reflux, and Recurrent Urinary Tract Infections

The relationship between detrusor instability, VUR, and UTIs has been firmly established by many authors.[15-18,63,70-76] It has long been known that a significant proportion of children with VUR have various bladder dysfunctions, and the converse is true—that is, reflux can be shown by micturating cystography in 15% of children with bladder dysfunctions.[76] Several studies have shown that treatment with urotherapy, including anticholinergics or oxybutynin, of a group of girls with dysfunctional voiding who also had VUR produced a significant reduction in the incidence of UTIs and the grade of reflux.[17] The mass of evidence points increasingly to the possibility that lower urinary tract malfunction, notably detrusor overactivity and bladder-sphincter dyssynergia, may act as an initiating and a perpetuating factor for VUR in older children, most of whom are girls.[18]

Bladder dysfunction does not cause reflux in all cases.[77] It has been suggested more recently that the reflux may be a causative factor of the bladder dysfunction, and the cure of reflux may actually cure the bladder dysfunction in some patients with persistent reflux and bladder dysfunction. A persisting reflux may also aggravate and perpetuate the bladder dysfunction and increase the risk of UTI in some children. It is important to treat both conditions, and if there is persistent reflux, a minimally invasive endoscopic treatment may be beneficial for the bladder dysfunction and the VUR.[78]

In the 1990s, urodynamic studies in infants with high grades of reflux also revealed various patterns of bladder dysfunction and have thrown new light onto our understanding of the pathogenesis of primary VUR in infancy.[10,16,30,79] There is a male predominance, and striking differences can be observed between male and female refluxing infants. Generally, male refluxers are characterized by considerably higher maximal voiding pressures and detrusor hypercontractility, which may represent a more pronounced form of detrusor-sphincter incoordination compared with age-matched female refluxers and healthy nonrefluxing infants. In contrast, in most female refluxing infants, a picture of an underactive bladder is seen. Reflux may occur during filling and voiding.[16,30] Reduction and normalization in the maximal voiding pressures in refluxing infants (mostly boys) were associated in two studies with early spontaneous resolution of reflux,[10,16] a finding not confirmed by Sillen and colleagues.[77]

Besides high voiding pressures, a significant proportion (>50%) of refluxing infants, again mostly boys, also displayed various abnormal urodynamic patterns, including detrusor instability and inefficient bladder emptying, that were not found in healthy "control" infants.[16,79] The results highlight the heterogeneity of the reflux problem and the possible role of various types of bladder dysfunction in the pathogenesis of primary VUR and recurrent UTIs in infants and in older children. It is of paramount importance that the management of high-grade VUR, especially when complicated by recurrent UTI, should entail proper assessment and tailored therapy for any underlying bladder dysfunctions.

Hinman Syndrome and Occult Neuropathic Bladder

Hinman and Baumann,[80,81] Allen,[82] and Dorfman and colleagues[83] first coined the terms *non-neurogenic neurogenic bladder* and *subclinical neurogenic bladder,* and later *Hinman syndrome,* to describe a presumably acquired form of bladder-sphincter dysfunction in children characterized by a combination of bladder decompensation with incontinence, poor emptying, and recurrent UTIs.[80-83] Most children also have significant bowel dysfunctions, including encopresis, constipation, and fecal impaction. In British literature, the condition is often referred to as *occult neuropathic bladder* after the article by Williams and associates.[84] The condition has all the clinical and urodynamic features typical of neuropathic bladder dysfunctions, but no neurologic abnormality can be shown.

It was initially hypothesized by Hinman and Baumann[80] that the condition could be ascribed to acquired psychologically abnormal behavior with voluntary incoordination between the detrusor muscle and the pelvic floor–external urethral sphincter complex during voiding. They supported their theory with a group of 13 boys having significant personality problems evidenced by anxiety, depression, and timidity. All these patients responded to a program of short-term anticholinergic medication, fecal disimpaction, counseling, and hypnotic suggestion therapy.[80,81,85] This notion has not received strong support from later studies, however.

Controversies still exist about whether a very subtle or occult spinal abnormality can occur to account for an isolated bladder neuropathy in a child who does not exhibit other somatic neurologic deficits and has normal magnetic resonance imaging of the spinal cord. Urodynamic studies often revealed marked sphincter overactivity and abrupt contractions of the pelvic floor as the child attempted to control incontinence from uninhibited bladder contractions. In its severe form, the vesicosphincter dyssynergia can cause full-blown bladder decompensation with day-and-night wetting, large postmicturition residues, recurrent UTIs, and significant damage to the upper tracts.[80-86] Imaging studies often reveal profound changes in the urinary tracts, with about two thirds of the children developing hydroureteronephrosis, and more than half having VUR. Nearly every patient has a grossly trabeculated, large-capacity bladder with a large postmicturition residual urine.

The condition probably represents an extreme end stage of detrusor-sphincter incoordination or dysfunctional voiding, most probably secondary to a subtle or occult organic neuropathy, although in some children an element of emotional disturbance may superimpose to interfere with normal voiding and complicate the issue further. It is conceivable that the bladder could decompensate, with its detrusor muscle losing contractility after long-standing functional outflow obstruction owing to sphincter overactivity, whether on an organic neuropathic or a behavioral basis, resulting in chronic distention with a large capacity and poor emptying efficiency. Treatment is control of infection and restoration of normal bladder storage and emptying functions.

Because of the similarities to neuropathic bladder dysfunction, the management strategy in these children generally follows very similar principles for the former condition. Standard urotherapy includes bladder retraining, pharmacologic bladder manipulation to target specific urodynamic abnormalities, and improvement of bowel function, especially the avoidance of severe constipation and fecal impaction; all have been shown to be effective. Biofeedback has also been reported to achieve good results.[87,88] In a multicenter prospective study in more than 200 children with non-neuropathic bladder-sphincter dysfunction reported in 2000 by Van Gool and associates[89] on behalf of the European Bladder Dysfunction Study Group, there were no statistically significant differences, however, in outcome between bladder rehabilitation with biofeedback and standard urotherapy. This disparity probably highlights the heterogeneity of the condition and further supports the view that management for these children should be individualized.[90] In many patients, prolonged clean intermittent catheterization may be required to improve detrusor contractility and bladder-emptying function.

Another piece of indirect evidence that a very subtle or occult neurologic lesion may account for some cases of "non-neurogenic neurogenic" bladder-sphincter dysfunction is the *Ochoa (urofacial) syndrome*. Children with this syndrome exhibit all the classic features of dysfunctional voiding, including urinary incontinence, recurrent UTIs, constipation, reflux, and upper tract damage, but in addition have a peculiar painful or apparently crying facial expression during smiling.[91,92] The condition has an autosomal recessive inheritance, and the gene has been located on chromosome 10. Urodynamic studies characteristically showed a sustained contraction of the external sphincter during voiding. The resulting severe bladder-sphincter dysfunction is often associated with a dismal outcome.

Of the 66 children reported by Ochoa,[92] 33% had renal functional impairment, 26% had hypertension, and 24% had end-stage renal failure. Five patients received renal transplants, and 17 died. Because the neural ganglia controlling the facial muscles are situated very close to the pontine micturition center, it is tempting to speculate that a small neurologic lesion located in this area, which is probably congenital in origin and genetically predetermined, may be responsible for the peculiar facial expression and the bladder dysfunction. Further studies in this direction may help to resolve some of the continuing dilemma.

Constipation and Bladder Dysfunction

It has long been recognized that children with dysfunctional voiding and recurrent UTIs often have associated bowel dysfunction, including constipation, fecal impaction, and encopresis, probably resulting from the close proximity of the chronic rectal dilation to the posterior wall of the bladder, interfering with the normal function of the lower urinary tract, resulting in bladder dysfunction, reflux, and UTIs.[93-96] In addition, it has been observed that large fecal impaction may induce significant detrusor overactivity and other bladder dysfunctions, which result in the urge syndrome, UTI, and reflux.[93-96] A high incidence of enuresis is found in children with UTI and constipation,[97,98] and treatment of the concomitant constipation resulted in cessation or improvement of incontinence. Animal studies have also revealed an increased predisposition to bacteriuria in rats with surgically induced fecal retention.[99] The evidence available so far strongly suggests that there is an important relationship between constipation, detrusor instability, reflux, UTI, and enuresis. Proper attention to the associated bowel dysfunction should form an integral part of the overall management of children with bladder dysfunctions.

Bladder Dysfunction and Nocturnal Enuresis

Primary nocturnal enuresis is a common disorder in children. Despite extensive research, there is still much controversy regarding its etiology, and it is now generally accepted that multiple pathologic factors are probably involved. Among others, a common finding is that the nocturnal urine output in many enuretic children is in excess of the bladder reservoir capacity during sleep at night.[100-102] Nocturnal polyuria can be either absolute—which is sometimes associated with a derangement of the circadian rhythm of antidiuretic hormone secretion—or relative—caused mainly by an increased propensity to detrusor contractions during sleep at night. The exact role of bladder dysfunction in the pathogenesis of primary nocturnal enuresis has until more recently remained largely controversial. Although some authors have observed markedly reduced voided volumes among enuretic children compared with age-matched nonenuretic controls, others have reported that enuretic episodes were triggered by a full bladder, and that bladder storage capacity in the enuretic children was completely normal.[103-105] Studies since about 1995 have very convincingly proved, however, that in a significant proportion of children with severe nocturnal enuresis, especially children who were refractory to conservative treatment and failed to respond to desmopressin therapy, there was a marked reduction in bladder storage capacity compared with age-matched healthy controls.[19,20,106-108]

It has been shown that other types of bladder dysfunctions, notably dysfunctional voiding, bladder overactivity, and marked detrusor hypercontractility with extremely high voiding pressures suggestive of an obstructive pattern, are common among enuretic children.[20] Overnight studies in enuretic children with simultaneous sleep electroencephalography and cystometry revealed marked detrusor overactivity only after sleep at night, but not during wakeful periods in the daytime.[14,19,20] This overactivity per se can result in a marked reduction in the nocturnal bladder storage capacity.[19,20,107,108] Because this pattern has not been observed in healthy nonenuretic subjects even during the newborn period, one may hypothesize that this could be due to a small neurologic lesion affecting a tiny area surrounding the vicinity of the pontine micturition center, the posterior hypothalamus (responsible for the secretion of antidiuretic hormone), and the locus caeruleus (which is thought to play an important role in the initiation of cortical arousal and the release of norepinephrine).[8,16,20]

Despite the high prevalence of underlying bladder dysfunctions among patients with severe, refractory primary nocturnal enuresis, many have no identifiable daytime urinary symptoms, including incontinence, frequency, and urgency. A detailed urodynamic study would reveal detrusor overactivity in 30% to 90% of patients, however. Our experience showed that many enuretic children with reduced voided volumes have learned, either consciously but more probably subconsciously, to restrain fluid intake during the daytime as an attempt to avoid the social inconvenience of urinary frequency and urge incontinence. This fluid restriction can often be easily spotted in a detailed home-recorded voiding diary showing an extraordinarily low fluid intake and infrequent, small-volume voiding. By giving these patients a standard fluid intake and then asking them to repeat a home recording of micturition frequency and urinary volume, one could easily obtain a highly reliable estimation of the storage capacity of the bladder and identify the patients with detrusor overactivity.[20,109]

To date, the bulk of evidence suggests that nocturnal enuresis is a heterogeneous condition consisting of a spectrum of disorders, and that various types of bladder dysfunctions probably contribute significantly to its pathogenesis, particularly in patients with severe symptoms who are refractory to treatment. Even in children with gross underlying bladder dysfunctions, nocturnal enuresis may be the only presenting manifestation, and a positive response to desmopressin therapy does not exclude such possibilities. These should be borne in mind in future management of patients with refractory primary nocturnal enuresis.

Etiologic Classification of Bladder Dysfunction

Dysfunction of the lower urinary tract in children can be secondary to derangement of nervous control, disorders of detrusor and sphincter muscle function, structural abnormalities, and other unclassified conditions.[23]

Derangement of Nervous Control

Conditions involving derangement of nervous control include congenital malformations of the central nervous system (e.g., myelomeningocele, spina bifida occulta, caudal regression syndrome, tethered cord syndrome); developmental disturbances (e.g., mental retardation, dysfunctional voiding, urge syndrome); and acquired conditions (e.g., cerebral palsy, progressive degenerative diseases of the central nervous system associated with spasticity, transverse myelitis, multiple sclerosis, vascular malformations, trauma of the spinal cord).

Disorders of Detrusor and Sphincter Muscle Function

Disorders of detrusor and sphincter muscle function include muscular dystrophy, neuronal dysplasia (megacolon-megacystis syndrome), and acquired conditions such as chronic bladder distention.

Structural Abnormalities

Structural abnormalities include congenital conditions (e.g., bladder exstrophy, epispadias, cloacal anomaly, ureteroceles, posterior urethral valves and other urethral anomalies, prune-belly syndrome) and acquired conditions (e.g., traumatic stricture or damage to the sphincter or urethra).

Other Unclassified Conditions

Unclassified conditions include giggle incontinence, Hinman syndrome, and Ochoa syndrome.

NEUROPATHIC BLADDER-SPHINCTER DYSFUNCTION

Dysfunction of the lower urinary tract resulting from an identifiable neurologic lesion constitutes a significant proportion of the clinical problems seen in pediatric urology.[110] In principle, any lesion that interferes with the afferent or efferent pathways between the bladder and the higher centers can result in neuropathic bladder-sphincter dysfunction. In contrast to in adults, however, most neuropathic bladder dysfunctions in infants and children are due to abnormal spinal column development, or myelodysplasia, and are very rarely caused by trauma or other disease conditions.[22,111] Other associated conditions include spinal dysraphism (including lipomeningocele, diastomyelia, dermoid cyst, or lipoma of the spinal cord with tethering of the filum terminale) and sacral agenesis.

Categorization of Neuropathic Bladder-Sphincter Dysfunction

Under normal circumstances, the bladder–external sphincter–perineal muscle complex works as a unit in a coordinated manner, allowing the storage of urine from the upper tract at low pressure and periodic, voluntary, and complete emptying. Control and coordination of these events occur at different levels of the central nervous system, converging at the sacral micturition center. The latter is developmentally abnormal in most children with myelodysplasia, which causes different types of bladder dysfunction. The neurogenic bladder may be deficient in the storage and the emptying function in various degrees.[112,113] Lower urinary tract dynamics in neuropathic bladders can be categorized according to two main factors, as follows[112-116]:

1. Detrusor contractility—normal, overactive, or inactive
2. External sphincter activity—normal (synergic or coordinated), overactive (dyssynergic or uncoordinated), or inactive

These elements can occur either alone or in various combinations. In a review of 188 children with myelomeningoceles followed from birth with serial urodynamic studies, Schulman and van Gool[90] reported that the detrusor activity was overactive, inactive, and normal in 55%, 38%, and 7%, whereas the sphincter activity was overactive, inactive, and normal in 59%, 34%, and 7%.

Detrusor-sphincter dysfunction in neuropathic bladders is not a static phenomenon and may change and evolve over time.[110,115,116] Changes in the urodynamic patterns can occur as a result of actual changes in the neurologic lesion itself (e.g., progressive tethering of spinal cord), or development of other associated lesions (e.g., syringomyelia). In addition, changes can be secondary to natural evolution of the bladder-sphincter function. The detrusor muscle may gradually lose its compliance with time because of the development of overactivity or because of increased collagen deposition in response to chronic outflow obstruction and elevated intravesical pressure, or a combination of both. Alternatively, the detrusor may become fatigued and lose its contractility, rendering the bladder into a decompensated, hypocontractile system with poor emptying efficiency. An isolated urodynamic study performed at any time in a child with neuropathic bladder-sphincter dysfunction may merely represent a cross-sectional snapshot of the whole developmental sequence of events, which can be fully revealed and understood only by long-term follow-up and serial assessment.

With the advent of urodynamic monitoring of intravesical pressures combined with pelvic floor electromyography and flow rate and videourodynamic studies, considerable progress has been made in the understanding of the pathophysiology of bladder-sphincter dysfunctions in children with myelomeningoceles, especially about the activities and coordination of the detrusor muscle and the external urinary sphincter during bladder filling and emptying. This urodynamic monitoring has not only permitted accurate delineation of the types of neuropathic bladder dysfunction, but also provided important prognostic clues to pediatric urologists for better planning of follow-up surveillance studies. This has contributed significantly to the improvement in the management of neuropathic bladders, making it now possible to tailor treatment to specific problems of individual patients.[110-114]

Finally, the bladder should not be viewed in isolation because a substantial proportion of children with myelomeningoceles have concomitant bowel dysfunction with various degrees of fecal impaction or incontinence or both. Fecal retention and a loaded rectum have a profound influence on the behavior of the bladder and must be effectively managed simultaneously. The elements of bowel dysfunction, constipation, fecal impaction, and incontinence must be properly considered in the evaluation of children with myelodysplasia and neuropathic bladder dysfunction.

Congenital Abnormalities of the Spinal Cord and Myelomeningoceles

Congenital abnormalities of the spinal cord, or myelodysplasia, account for most neuropathic bladder dysfunctions seen in children. They consist of a heterogeneous group of developmental anomalies that include occult spina bifida, meningocele, myelomeningocele, lipomeningocele, primary tethered cord, diastematomyelia, intradural lipoma, dermoid cyst, syringomyelia, and sacral agenesis.[112,117] These anomalies are associated with distortion of the developing neural tissues, with subsequent damage to the spinal cord. Closed spinal defects may be heralded at birth by an overlying skin lesion, such as a skin dimple, a hairy tuft, or a lipoma, or a limb deformity resulting from the associated neurologic abnormalities. Such defects might not be recognized, however, until the onset of urinary incontinence, UTI, gait abnormalities, and an inability to squat or other orthopedic problems in later childhood in association with growth of the spine or increased mobility.

Early and comprehensive urodynamic evaluation of the lower urinary tract has substantially improved the management of children with myelomeningoceles. It has been recommended that urodynamics be performed as a routine test before and after closure of the spinal defect.[118,119] Because the neurologic lesions are often not static, but may change with the growth and development of the child, it is prudent that repeated urodynamic assessment of the lower urinary tract function be performed.[115,116,119] A leak point pressure of greater than 40 cm H_2O (more recently suggested to be a maximum of 25 cm H_2O) poses a statistically increased risk of developing reflux or hydronephrosis or both with progressive deterioration of renal function,[115,118-121] and there is an increased risk of developing bladder trabeculation and high-pressure reflux that could compromise upper tract drainage and function when outlet resistance is elevated and intravesical pressure increases to greater than 40 cm H_2O.[115]

Detrusor-Sphincter Dyssynergy

Detrusor-sphincter dyssynergy is a major problem in children with myelomeningoceles and occurs when the external sphincter fails to relax or increases its activity during a detrusor contraction.[122] As described earlier in this chapter, some degree of detrusor-sphincter incoordination, which is associated with high voiding pressure and interruption of flow but with no impairment of overall bladder emptying, can be seen even in healthy infants during the first year of life.[8,16,34,43,44] In children with neuropathic bladder, the detrusor-sphincter dyssynergia manifests in a much more pronounced manner, and together with pelvic floor overactivity may produce significant functional outflow obstruction, leading to elevated intravesical pressure, upper tract dilation, high-pressure VUR, and incomplete bladder emptying. This obstruction predisposes to recurrent UTI, and together the adverse hydrodynamic factors and infections can cause substantial damage to the upper tract within a short time.[122,123]

When bladder outlet resistance is chronically increased because of sphincter dyssynergia, bladder compliance is likely to decrease as a result of detrusor overactivity and progressive collagen deposition, which can occur alone or in combination.[124] This situation results in a small, contracted, poorly compliant bladder with continuously elevated intravesical pressures during filling and emptying. The decreased compliance not only may lead to increasing incontinence, but also may produce a considerable degree of functional obstruction to upper tract drainage and can be of crucial importance in the predisposition to renal functional impairment. Bladder emptying may be maintained by progressive compensatory detrusor hypertrophy and overactivity until the detrusor muscle becomes fatigued, and bladder decompensation occurs. The bladder then loses its contractility, increases substantially in capacity, and fails to empty. Urinary retention occurs, and the resulting residual urine predisposes to recurrent infections if artificial emptying by clean intermittent catheterization is not implemented. The combination of high intravesical pressures, VUR, and UTI allows transmission of the elevated pressures and pathogenic bacteria to the upper tract and heralds progressive renal deterioration.[121]

Protection of kidney function in children with neuropathic bladders depends on the successful maintenance of good bladder compliance to allow filling at low pressures and satisfactory bladder emptying. Early urodynamic studies are necessary to identify infants who are at risk for upper tract deterioration as a result of functional infravesical obstruction from detrusor sphincter dyssynergia or poor bladder compliance owing to detrusor hypertonicity, or often a combination of both.

Sphincter and Pelvic Floor Inactivity

The main problem in patients with inactivity of the external sphincter and pelvic floor musculature is urinary incontinence. The amount and frequency of leakage are determined by the activity of the detrusor and the residual outlet resistance. If there is coexisting detrusor overactivity, frequent leakage is expected with uninhibited detrusor contractions, resulting in a marked decrease in the voided volumes. Alternatively, if sphincter inactivity is combined with detrusor inactivity, overflow incontinence with continuous dribbling occurs. Because of the poor outlet resistance, urine leakage tends to appear in response to any detrusor contraction or elevation in intravesical pressure, maintaining the pressure inside the bladder at a low level. Consequently, high-pressure VUR and recurrent UTI are not commonly seen, and damage to the upper tract is not an immediate hazard.

Management for sphincter inactivity in combination with detrusor inactivity should start with means to enhance regular and complete bladder emptying, usually by clean intermittent catheterization.[125] Frequently, this measure alone helps to ameliorate the incontinence problem substantially to a more socially acceptable level, particularly if the bladder volume is adequate. Manual expression of urine by suprapubic pressure (Credé maneuver) is not satisfactory because the bladder neck tends to be displaced caudally, resulting in kinking of the proximal urethra and incomplete bladder emptying. If complete dryness cannot be achieved by clean intermittent catheterization alone, various surgical procedures to enhance the bladder outlet resistance, such as injection or formal reconstruction of the bladder neck, insertion of an artificial sphincter, and bladder neck suspension, can be considered with or without concomitant bladder augmentation depending on whether the voided volumes are sufficient.

Children with sphincter inactivity in combination with detrusor overactivity can be managed first with pharmacologic manipulation (e.g., anticholinergics) to reduce the unstable contractions. Pharmacologic agents alone commonly may lead to an increase in bladder volume, in conjunction with a significant reduction in urine leakage. Failing this, other measures to increase the bladder capacity (e.g., bladder augmentation) may be necessary in combination with surgical procedures to enhance the bladder outlet resistance after the child has acquired the proper techniques for clean intermittent catheterization. The aim is to convert the bladder from a poorly compliant, small-capacity system to a more compliant system with adequate storage capacity and good outlet resistance.

Neuropathic Bladder and Vesicoureteral Reflux

VUR occurs in approximately 30% of newborns with neuropathic bladders secondary to myelodysplasia.[116] An elevation in intravesical pressures associated with neuropathic bladder dysfunction magnifies the potential damage that may result from reflux by providing the hydrodynamic force needed to drive the pathogenic bacteria into the kidney parenchyma, inducing pyelonephritis and renal scarring.[126] Urodynamic studies have indicated that the high-end filling pressures in decompensated bladder, especially in children with a combination of sphincter and detrusor overactivity, initiate and perpetuate the high-pressure reflux. It has been postulated that the high intravesical pressures may contribute to weakening of the detrusor musculature support at the ureterovesical junction, which is crucial for the normal antireflux mechanism. Inefficient bladder emptying with substantial postmicturition residues also predisposes to recurrent UTI and aggravates further the damage to the upper tract.[127] A significant reduction in the glomerular filtration rate occurring at high bladder pressures has been shown in myelodysplastic children.[121]

VUR occurring in children with neuropathic bladders is largely secondary to the adverse urodynamic factors, rather than a primary event. Treatment should focus mainly on the underlying bladder dysfunction, rather than on stopping the reflux.

CONCLUSION

Despite extensive clinical and animal research, the exact neurologic mechanisms of the development of micturition control from newborn to infancy and later childhood, and the pathophysiologic pathways that are involved in various types of bladder dysfunction have remained largely unclear. It is, however, certain that the bladder and the brain talk with each other all the time as early as the fetal stage, and that there are extremely rapid and extensive changes and modulation of micturition reflexes during the early postnatal period, leading to copious potentials for developmental errors and voiding dysfunctions. Since the 1990s, we have learned that normal and abnormal bladder function are much more dynamic than we had previously believed. New investigative tools and research have allowed us to study with much greater detail and precision the various components, including neurologic, muscular, urodynamic, and hormonal mechanisms, that may intricately interact to produce different patterns of bladder dysfunctions and their relentless changes. A new systematic classification has been proposed by the International Continence Society,[62] described in this chapter, to clarify bladder dysfunctions.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 28

PRAGMATIC APPROACH TO THE EVALUATION AND MANAGEMENT OF NON-NEUROPATHIC DAYTIME VOIDING DISORDERS

Ulla Sillén and Anna-Lena Hellström

To understand the pathophysiology of functional daytime voiding disorders in children, normal development of bladder and sphincter control must be understood. This chapter deals mainly with the evaluation and management of these problems. For more information on the pathophysiology from the normal developmental point of view, see Chapter 27.

ACHIEVEMENT OF DAYTIME URINARY CONTROL

Micturition is modulated by higher centers from birth, but it is not until between the age of 1 and 2 years that a child is able to show bladder awareness and, as a first step, to report having voided or being in the process of voiding. During the second and third years, the conscious sensation of bladder filling develops, together with language proficiency, and the child can more easily express a need to void. By age 4 years, most children control their voiding and can initiate a void at will, and inhibit micturition if it is an inappropriate place or moment. The child has acquired the ability to control the voiding process voluntarily, including the external urinary sphincter and the ability to initiate or inhibit the micturition reflex.[1]

Active toilet training can probably influence the point in time at which the child becomes dry during the day, but not the time at which voluntary control over the entire voiding process develops. Studies made before the era of disposable diapers report a median age for daytime dryness of 2 years, whereas in more recent studies the corresponding age is 3 years. In the earlier and more recent studies, the age for full-time daytime control is 4 years, which indicates that most children are mature enough for independent volitional control of voiding at this age. Toileting with the support of a parent or other caregiver is probably possible at an earlier stage in most children.[1]

The process of gaining control over bladder and sphincter function is complex, and it is understandable that this series of complex events is highly susceptible to the development of various types of dysfunction. Toilet training has to be carried out in a positive way; otherwise, it can have a negative result. Psychological difficulties at this age also have been reported to influence the age at which a child is dry.

EPIDEMIOLOGY

Symptoms typical of functional bladder disturbances, such as postponement of voiding, urgency, and leakage of urine, have been shown to be common even in healthy children before age 5 to 6 years, but not on a daily basis.[1,2] From this point of view, age 7 is an appropriate time for the investigation of prevalence of functional non-neurogenic bladder disturbances. Most epidemiologic studies do not look specifically at the different diagnoses associated with functional disturbances, such as overactive bladder (OAB), dysfunctional voiding, and postponement of voiding, but investigate only the prevalence of urinary incontinence. From the studies available, it is difficult to draw conclusions about the prevalence of urinary incontinence because different studies use different definitions and criteria. Examples of the latter are variation in frequency of incontinence episodes and inclusion of daytime incontinence only or daytime and nighttime incontinence.

The mean prevalence of daytime wetting at age 7 years for all children is approximately 4.5% (range 3.2% to 6.7%), according to cross-sectional studies.[3,4] When only children with frequent episodes of urinary incontinence—more than once a week—are included, the corresponding figure is 2.5%. For children 15 to 17 years old, the mean for all kinds of daytime wetting is 2% (range 1.2% to 3%); the mean for children at this age with more than one episode a week is only 0.3%.[5,6] The spontaneous and treated cure rate is approximately 6% per year, including all daytime wetting, and the corresponding figure for children with frequent wetting is 9%.

All functional urinary incontinence is more common in girls in all age groups. From the prevalences found in different studies, it can be assumed that incontinence is 1.5 times more common in girls than in boys at age 7 years. At age 16, the difference is even more pronounced, with incontinence 5 to 10 times more common in girls.

Risk factors for functional voiding disorders are listed in Table 28-1. A positive family history has been reported to increase the risk of daytime incontinence.[2,7] Psychopathology has also been shown to be a risk factor. Lettgren and associates[8] have found significant increases in attention problems and delinquent behavior to be associated with a certain type of daytime wetting in children (voiding postponement) using the Child Behavior Checklist. Minor neurologic dysfunctions, such as attention-deficit/hyperactivity disorder, carry an increased risk of daytime incontinence by a factor of 9.[9] Children with mental developmental delay or retardation are also at increased risk.

EVALUATION

The initial evaluation of children with daytime voiding disorders should include voiding and bowel history taking, physical examination, urinalysis, a bladder diary, and in most cases urinary flow and residual urine evaluation using ultrasound, and quantification of urine loss (Table 28-2). These noninvasive measures often provide insights enabling the clinician to categorize the child's urinary problems in a way that allows for a preliminary diagnosis and management. In a few incontinent children, these noninvasive assessments yield uncertain results, or results suggesting deviations from normal function. In these situations, invasive investigations, such as voiding cystourethrography (VCUG), invasive urodynamics, renal scans, urography, and cystourethroscopy, are indicated.

Table 28-1 **Risk Factors for Non-neurogenic Daytime Voiding Disorders**

Family history
Sociocultural factors
Psychopathology
Minor neurologic dysfunction (e.g., attention-deficit/hyperactivity disorder)
Developmental delay
Sexual abuse

Table 28-2 **Noninvasive Investigations in All Children with Functional Daytime Voiding Disorders**

Voiding and bowel history taking
Physical examination
Urinalysis
Bladder diary
Urinary flow and residual urine
Continence test

History

For the pediatric age group, the history is obtained jointly from parents and child. The history should include a general health history and a specific voiding history. The general history should include questions of relevance to familial disorders, neurologic and congenital abnormalities, and relevant surgery and menstrual and sexual functions (in pubertal and older children). Information about urinary tract infections (UTIs) is also important, as are any previous problems related to the urinary tract, such as vesicoureteral reflux (VUR).

A validated questionnaire is a very useful tool in taking a voiding history, and in structuring the history taking or at least providing a checklist (Fig. 28-1). If possible, the child should be addressed as the patient and questioned directly, to elucidate what symptoms are most problematic for the child.

Information about onset (primary or secondary) of the problems should be obtained. Failed prior treatment attempts should be noted. Voiding *frequency* and *voided volumes* must be determined. To be able to count the number of voids, it is recommended that the voiding be related to special routines: "Do you void directly after getting up in the morning?" "Do you void during school hours?" For correct information about frequency and volume of voiding, however, a bladder diary is mandatory in addition to the verbal assessment.

Incontinence episodes during the day and night should also be estimated: How often? How much (a few drops, damp or wet underwear, need to change, use pads)? When does the leakage occur? Does it occur together with *urgency* attacks? Does it occur with *giggling*? Is it unrelated to such events? At what time of the day does it occur? *Urgency* attacks and *holding maneuvers,* such as squatting, crossing one's legs, or standing on tiptoes, should be noted. Voiding symptoms, such as *hesitancy, staining,* and *weak or intermittent stream,* should also be recorded in the voiding history.

History taking should include assessment of bowel function. A similar proactive process using a questionnaire should be followed for defecation and fecal soiling. Stool habits, including interval, size, and consistency, should be investigated. Is there soiling, how often, and in what situations? Have any medications been used to treat bowel function?

Physical Examination

In addition to a general pediatric examination, the physical examination should include the assessment of perineal sensation, the perineal reflexes from the sacral segments S1-S4 (standing on toes, bulbocavernosus), and anal sphincter tone and control. Special attention should be paid to inspection of the genital region and of the urethral meatus. Asymmetry of buttocks, legs, or feet, and other signs of occult spinal dysraphism in the lumbosacral area (subcutaneous lipoma, skin discoloration, hair growth, and abnormal gait) should be investigated specifically. In examining the abdomen, the presence of a full bladder or full sigmoid or descending colon with a history of constipation is a significant finding.

Urinalysis

Urinalysis with a dipstick is essential to exclude infection, glucosuria, and proteinuria. Although urinalysis can be helpful in signaling infection, UTI can reliably be excluded only with a urine culture.

Noninvasive Diagnostic Techniques

Frequency and Volume Charts: Bladder Diary

The recording of voids and bladder-related symptoms at home under normal conditions is crucial for the assessment of lower urinary tract function in childhood, and is relevant for the attainment of bladder control. The frequency/volume chart is a detailed diary recording fluid intake and urine output over 24-hour periods. The chart gives objective information on the number of voidings, the distribution of day and night voids, and voided volumes and episodes of leakage (Table 28-3). To obtain a complete picture, defecation frequency or soiling or both should also be recorded. The diary should be kept for 2 to 3 days, of which at least 1 day should be a weekday (Fig. 28-2). Using the frequency/volume chart, the child's functional bladder capacity may be assessed as the largest voided volume, with the exception of the morning micturition, which actually represents night bladder capacity.

A bladder diary provides helpful information in the assessment of the child's voiding disorder because it is often difficult for the child and the parents to provide a reliable voiding history when it comes to number of voids, number of leakages, and time of drinking. The voiding diary is not only an important instrument in the diagnosis of the child's voiding disorder, but also important in treatment, as a tool assuring the child that he or she is making progress. For the latter reason, filling out the chart should be the responsibility of the child whenever possible; the parents can provide assistance and support. It is also a tool to make the child take an active part in the treatment, and is part of the motivational process.

Quantification of Urine Loss

Subjective grading of incontinence may not indicate the degree of dysfunction. For objective grading, the 12-hour pad test and frequency/volume charts are validated instruments (Fig. 28-3). In children, the 12-hour pad test also gives information about fluid intake. The pad test is complementary to the bladder diary, which describes more the frequency of incontinence and the distribution of wetting episodes than the quantities of urine loss.

The practical accomplishment of a 12-hour pad test includes change of weighed pad every hour. Leakage is equal to the increase in weight of each respective pad. The most practical arrangement is that the family gets a bag with 12 weighed pads, each in a plastic bag. The bag with the pads should not be placed in the bathroom to avoid the risk of voiding in the toilet when changing pads. The pads should be returned to the caregiver after use, with each pad securely sealed in its plastic bag.[10] The information obtained is summarized in Table 28-4.

Stool and Diet Diary

A stool and diet diary can be used for any child with a daytime voiding disorder, if the history indicates bowel-related problems. Plain imaging of the abdomen is sometimes helpful in determining the degree of constipation. Colonic transit time is probably a better way, however, to match clues from the history with the degree of constipation.

VOIDING HISTORY

Name ____________________

Date of birth ________________ Date ____________

Holding			
Awareness of need	Daily ☐	< Once a day ☐	No ☐
Hold pattern	Daily ☐	< Once a day ☐	No ☐
Need to be reminded	Daily ☐	< Once a day ☐	No ☐
Urgency	Daily ☐	< Once a day ☐	No ☐
Holding maneuvers	Daily ☐	< Once a day ☐	No ☐
Void at school	Daily ☐	< Once a day ☐	No ☐
Wake up during night to void	Daily ☐	< Once a night ☐	No ☐
Emptying			
Starting difficulties	Daily ☐	< Once a day ☐	No ☐
Straining	Daily ☐	< Once a day ☐	No ☐
Interrupted urinary flow	Daily ☐	< Once a day ☐	No ☐
Position Sitting	Yes ☐	No ☐	Varies ☐
Urinary stream	Ample ☐	Thin ☐	
Pain	Daily ☐	< Once a day ☐	No ☐
When	Start ☐	During ☐	After ☐
Where	Bladder ☐	Urethra/ meatus ☐	Flank/ back ☐
How	Smarting ☐	Pain ☐	Spasm ☐
Urinary tract infection		No ☐	Cy ☐
		Py ☐	ABU ☐

Bowel function

Bowel movements	Daily or every other day ☐	3 times a week ☐

Consistency according to Bristol scale	1 ☐	2 ☐	3 ☐	4 ☐
	5 ☐	6 ☐	7 ☐	

Laxatives ____

Fecal incontinence	Daily ☐	< Once a day ☐
	< Once/week ☐	No ☐
	Soiling ☐	Encopresis ☐

Figure 28-1 Voiding history questionnaire.

(Continued)

Incontinence (daytime)

Incontinence?	Yes	☐	No	☐
Type	Primary	☐	Secondary	☐
When	At urge	☐	At giggle	☐
	At stress	☐	Unknown reason	☐
How	Drop	☐	Small spot	☐
	Large spot	☐	All	☐
How often	Once a day	☐	1 once a week	☐
	Once a month	☐		
Earlier treatments?	Yes	☐	No	☐
What	Regimen	☐	Detrusor relaxant	☐
	Other	☐		
Treatment efficacy	Good	☐	Improved	☐
	Bad	☐		
Heredity	Parents/siblings	☐	No	☐

Incontinence (night/enuresis)

Incontinence?	Yes	☐	No	☐
Type	Primary	☐	Secondary	☐
How	Small spot	☐	Everything	☐
How often	Once a night	☐	Once a week	☐
	Once a month	☐		
Arousal	When voiding	☐	Afterwards	☐
	Does not wake up	☐		
Earlier treatment	Yes	☐	No	☐
What	Alarm	☐	Desmopressin	☐
	Regimen	☐	Detrusor relaxant	☐
Treatment efficacy	Good	☐	Improved	☐
	Bad	☐		
Number of dry nights ______	(no/2 weeks)			
Heredity	Parents/siblings	☐	No	☐

Voiding diary

Number of voidings (mean)	______ no/day	Largest day volume	______ mL
Shortest interval	______ h	Number of leakage (mean)	______ no/day
Largest morning volume	______ mL	Drink intakes (mean)	______ mL/day
Diaper (night weight)	______ mL	Entire night volume	______ mL

Residual-flow measurement

Flow curve	Bell/tower	☐	Staccato	☐
	Plateau	☐	Interrupted	☐

Voided volume	______mL	Flow time	______sec
MaxQ	______mL/sec	Residual urine	______mL

Suggested treatment

Regimen	☐	CIC	☐	Enuresis alarm	☐
Desmopressin	☐	Detrusor relaxant	☐	TENS	☐
Biofeedback	☐	Other treatment	☐	____________________	

Figure 28-1, cont'd.

Table 28-3 Voiding Diary

Time for voiding
Time for leakage
Number of voids
Number of incontinence episodes
Voided volumes
Fluid intake and distribution
Bowel movements

Urinary Flow

Voiding should be analyzed in detail in all children with daytime incontinence. The investigation is mainly used as a diagnostic instrument, but also can be used in treatment (e.g., as flow biofeedback). Registration of the urinary flow rate during voiding is becoming a standard office procedure. In these cases, measurement of urinary flow is done as a noninvasive procedure with filling of the bladder by diuresis (spontaneous or forced by instructions of standardized excessive drinking). Flow patterns and rates should be repeated if abnormal because sometimes several recordings are needed to obtain consistency.

A bell-shaped flow curve is present in 99% of healthy children.[11] If the voided volume is less than 50% of the expected capacity, the flow curve can be bell-shaped even if there is an obstruction because a small volume creates a low maximal flow, but with a bell-shaped curve. The voided volume must be more than 50% of expected capacity for a urinary flow examination to be reliable. Another suggested rule is that the square of the maximal flow should exceed the voided volume.[12] Otherwise, the volume may be too low, or there may be an obstruction.

Urinary flow may be described in terms of rate and pattern, and may be continuous, intermittent (fractionated), or staccato. An intermittent flow pattern shows interruption of the flow curve, whereas in staccato voiding the flow does not stop completely, but fluctuates because of incomplete relaxation of the sphincter. The parameters of interest in a urinary flow investigation are pattern of the curve, voided volume, maximal flow rate, and voiding time (Table 28-5). For illustrations of the different flow curves, see Chapter 9.

Postvoid Residual Urine

The identification or exclusion of postvoid residual is an integral part of the study of micturition. Residual urine is usually assessed with ultrasound after uroflow measurement. Healthy children after toilet training age empty their bladders completely with each voiding. The inevitable delay of a few minutes after finishing voiding until an ultrasound calculation can be made would result in the bladder refilling with up to 5 mL, which is the upper value of residual accepted as completely normal. In case of a longer time delay, this can be compensated for by subtracting 1 to 2 mL from the measured residual for every minute beyond 5. A range of 5 to 20 mL may be associated with insufficient emptying, but can also be occasional, and in these cases the investigation must be repeated. More than 20 mL of residual on repetitive occasions indicates abnormal emptying.

It is sufficient to use a bladder scanner when investigating older children, in whom higher residual volumes can be expected. In infants and young children, however, in whom small volumes must be identified, a scanner is insufficient, and more advanced ultrasound equipment must be used. The formula used for calculation of volume of a full or almost full bladder is multiplication of length, width, and depth, divided by 2, because the bladder has an oval form when filled. When measuring residual urine, the volume seems to correspond better to the same formula but without division by 2 because the bladder has a more quadratic form at low filling.[13,14]

Invasive Diagnostic Techniques

Diagnosis and successful management of most pediatric patients with daytime voiding problems do not require invasive diagnostic studies. Whether invasive diagnostic procedures are necessary is decided by the results of the noninvasive procedures. Invasive procedures should be used only if the outcome would influence management. Symptoms indicating a need for further diagnostic procedures are voiding frequency of three or fewer voids per day, straining, weak urinary stream, previous febrile UTI, continuous dribbling incontinence, or previously identified VUR. Findings that suggest a need for invasive diagnostic techniques are signs of occult spinal dysraphism at physical examination, a plateau-shaped flow curve typical for structural bladder outlet obstruction, intermittent flow suggesting detrusor-sphincter dyscoordination, a clinically significant postvoid residual at repeated occasions, and continence test indicating continuous dribbling. Invasive diagnostic techniques are indicated when noninvasive procedures raise suspicion of neurogenic detrusor-sphincter dysfunction, obstruction (posterior urethral valves), genitourinary abnormalities (e.g., epispadias, ectopic ureter in girls), advanced non-neurogenic detrusor-sphincter dysfunction (dilating VUR or febrile UTI or both), or significant postvoid residuals.

Voiding Cystourethrography

VCUG is indicated in children with recurrent UTIs to detect reflux and in children with an abnormal flow pattern to detect bladder outlet abnormalities (e.g., valves, strictures). In children with non-neurogenic detrusor-sphincter dysfunction and in children with the same dysfunction but of neurogenic origin, the proximal urethra may show a “spinning top” configuration during filling or voiding. With detrusor and pelvic floor muscles contracting at the same time, the detrusor contraction dilates the proximal urethra down to the level of the forcefully closed external sphincter.[15]

Urodynamics

Invasive urodynamic investigations should be performed only if the outcome has consequences for treatment. Such studies are not required in most neurologically intact children with urinary incontinence. For definitions and descriptions of the methods available, see Chapter 9.

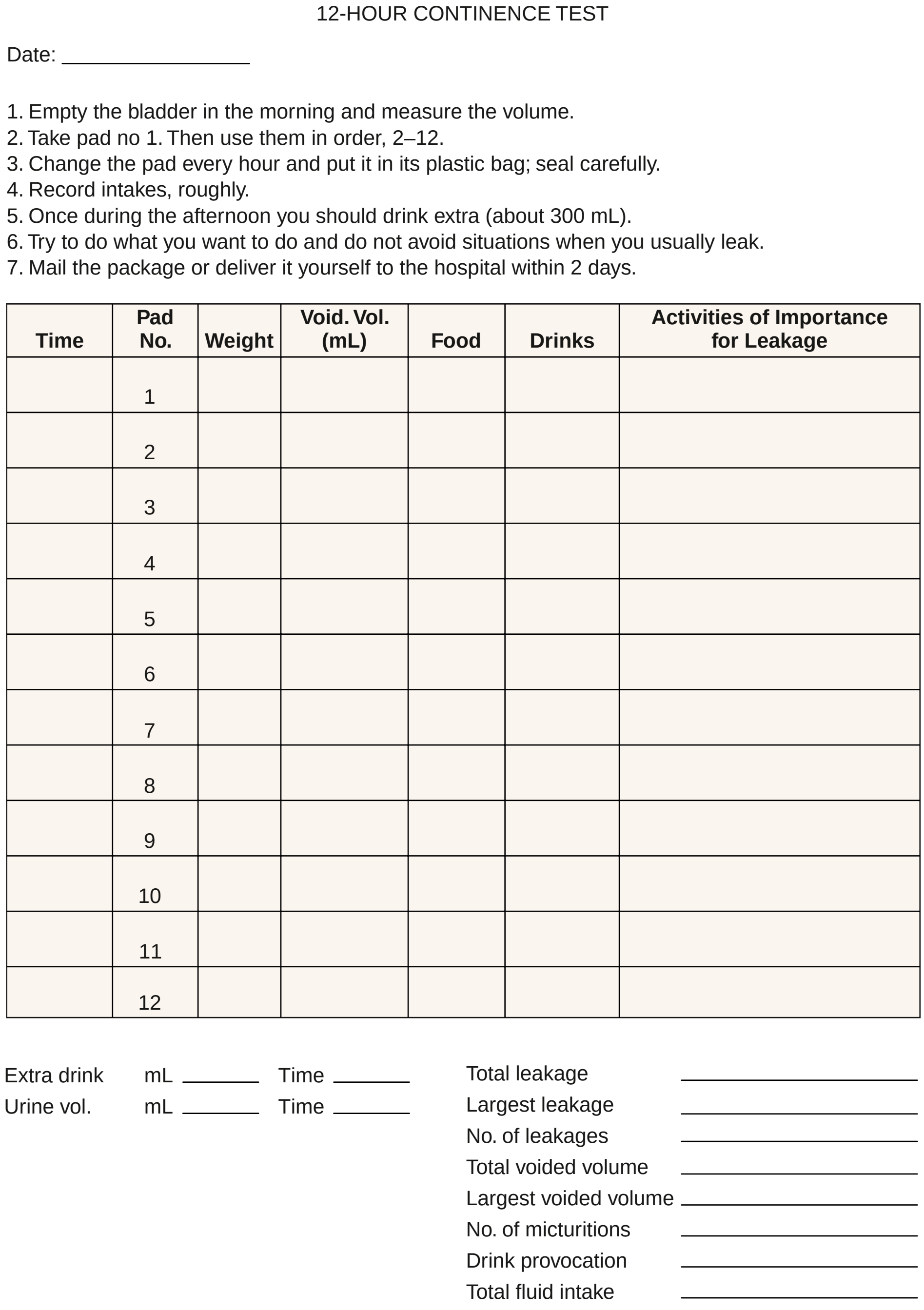
The main indication for invasive urodynamic studies in children with functional daytime voiding disorders is the need to exclude neurogenic bladder dysfunction (Table 28-6). If there is any symptom (e.g., secondary voiding dysfunction in older children, worsening of symptoms) or finding (e.g., lower back abnormalities, neurologic findings) making neurogenic bladder dysfunction a possible differential diagnosis, a cystometric investigation should be performed. In children with severe dysfunctional voiding, a neurogenic cause of the overactivity in the pelvic floor during voiding must be excluded. Underactivity of the detrusor is another diagnosis that can be excluded or confirmed with urodynamic studies

THREE-DAY VOIDING DIARY

Name:_________________________________

Date	Voiding Time Volume/mL	Dry/Wet	Drinks (mL)	Bowels	Date	Voiding Time Volume/mL	Dry/Wet	Drinks (mL)	Bowels	Date	Voiding Time Volume/mL	Dry/Wet	Drinks (mL)	Bowels
Time					Time					Time				
Night					Night					Night				
05 a.m.					05 a.m.					05 a.m.				
06 a.m.					06 a.m.					06 a.m.				
07 a.m.					07 a.m.					07 a.m.				
08 a.m.					08 a.m.					08 a.m.				
09 a.m.					09 a.m.					09 a.m.				
10 a.m.					10 a.m.					10 a.m.				
11 a.m.					11 a.m.					11 a.m.				
12 p.m.					12 p.m.					12 p.m.				
01 p.m.					01 p.m.					01 p.m.				
02 p.m.					02 p.m.					02 p.m.				
03 p.m.					03 p.m.					03 p.m.				
04 p.m.					04 p.m.					04 p.m.				
05 p.m.					05 p.m.					05 p.m.				
06 p.m.					06 p.m.					06 p.m.				
07 p.m.					07 p.m.					07 p.m.				
08 p.m.					08 p.m.					08 p.m.				
09 p.m.					09 p.m.					09 p.m.				
10 p.m.					10 p.m.					10 p.m.				
11 p.m.					11 p.m.					11 p.m.				

Figure 28-2 Three-day voiding diary form.



12-HOUR CONTINENCE TEST

Date: ________________

1. Empty the bladder in the morning and measure the volume.
2. Take pad no 1. Then use them in order, 2–12.
3. Change the pad every hour and put it in its plastic bag; seal carefully.
4. Record intakes, roughly.
5. Once during the afternoon you should drink extra (about 300 mL).
6. Try to do what you want to do and do not avoid situations when you usually leak.
7. Mail the package or deliver it yourself to the hospital within 2 days.

Time	Pad No.	Weight	Void. Vol. (mL)	Food	Drinks	Activities of Importance for Leakage
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					

Extra drink mL _______ Time _______
Urine vol. mL _______ Time _______

Total leakage ____________________
Largest leakage ____________________
No. of leakages ____________________
Total voided volume ____________________
Largest voided volume ____________________
No. of micturitions ____________________
Drink provocation ____________________
Total fluid intake ____________________

Figure 28-3 Twelve-hour continence test form.

only. Symptoms that might be an indication for such a problem, possibly of non-neurogenic or neurogenic origin, are straining at voiding, fewer than three voids a day, fractionated flow curve, or high postvoid residual. In children with recurrent UTI and daytime voiding symptoms, the recommended VCUG sometimes shows increased bladder wall thickness and trabeculation, which is also an indication for urodynamic studies.

The most important indication is probably in patients in whom conventional treatment of daytime voiding disorders is unsuccessful. Even if the investigation only confirms the diagnosis from the noninvasive studies, it is often reassuring for the patient and the parents. The cystometric curve also can be used to help the child understand better what happens in the bladder, as a biofeedback lesson.

Other Imaging Studies

When symptoms and findings including the cystometric results suggest a neuropathic bladder, a magnetic resonance imaging (MRI) study of the lumbosacral spine or referral to an appropriate specialist should be carried out, to exclude occult spinal dysraphism. In patients who fail to respond to conventional therapy and who are investigated to exclude a neurogenic bladder dysfunction but without any other objective findings, the risk of having occult spinal dysraphism is small, however, according to studies by Khoury and colleagues.[16]

Ultrasound of the upper urinary tract is included in the investigation of children with daytime wetting as a first step, when further investigations are warranted. It is now more or less routinely used in children with incontinence that does

Table 28-4 Pad Test

- Leakage volumes
- Total leakage volume
- Leakage-free interval
- Activities that influence leakage volume

Table 28-5 Urinary Flow

- Voided volume
- Maximal flow rate
- Flow time
- Voiding time
- Curve pattern
  - Bell-shaped
  - Staccato or irregular
  - Fractionated or intermittent
  - Obstructed

not respond directly to conventional therapy. It also should be performed in all cases with UTI.

GENERAL AND SPECIFIC TREATMENT INTERVENTIONS

The treatment of functional bladder disturbances is considered suitable from age 5 and older because the child is then normally able to void at will and to postpone voiding in a socially acceptable manner. By this age, daytime and nighttime involuntary wetting becomes a social problem.

Bowel Regimen

Overt constipation should be dealt with before embarking on treatment of incontinence or detrusor-sphincter dysfunction. If history indicates fecal retention, or if there is soiling, treatment should be instituted for achievement of normal bowel habits before starting treatment of urinary incontinence. The regimen should include the following:

- Explanation of soiling
- Toileting program
- Diet and fluid intake
- Laxatives

In 95% of cases, soiling is attributable to fecal retention, which should be explained to the patient and the parents. This often is a relief to the child because this connection has not earlier been believed.[17] Establishing a normal, regular pattern of bowel evacuation is a key to eventual success for children with soiling. Charts should be used.

A well-balanced diet with reasonable fiber intake is likely to be helpful. Excessive consumption of milk should be prohibited, and the overall fluid intake should be increased.

There is a general consensus that children with constipation and overflow soiling require laxative treatment, with the aim of evacuating retained stool and maintaining regular bowel activity. Over the last few years, osmotic laxative treatment with macrogols (polyethylene glycol variations, with and without electrolytes) has been shown to be effective and safe in large doses for initial clearing out and in smaller doses for maintenance.[18] Long-lasting constipation problems often have a functional explanation, such as unwillingness to defecate. The habit of always trying to hold must be overcome. A program based on principles similar to those used in urotherapy can be employed.

Table 28-6 Indications for Invasive Urodynamic Studies in Functional Voiding Disorders

- Neuropathic bladder dysfunction
  - Severe dysfunctional voiding
  - Secondary disorders in older children
  - Neurologic symptoms and findings
    - Asymmetry of buttocks or feet
    - Signs in the lumbosacral area (e.g., hair growth)
    - Abnormal gait
- Underactive detrusor (neurogenic or functional)
  - <3 voids a day
  - Fractionated flow curve
  - High postvoid residual
- Non-neurogenic neurogenic bladder (Hinman syndrome)
- Therapy-resistant voiding disorders

Urotherapy or Bladder Rehabilitation

Urotherapy or bladder rehabilitation is still quite a new concept, developed since the late 1970s.[19,20] It is defined as treatment aimed at normalizing bladder function and preventing further functional disturbances. This treatment includes stimulation of the child to cooperate actively in the treatment process (learning and practice) and includes evaluation of the child's bladder function and daily habits. Urotherapy is based on behavioral therapy; the child has to modify his or her habits. This requires cognitive components: the child and parents have to understand the coherence of the situation, including the function of the bladder, fluid intake, frequency of micturitions, and factors in daily life affecting bladder function. These cognitive components must be covered when creating an individual program for each child. Urotherapy can be divided into standard urotherapy and specific interventions in the urotherapeutic setting.

Standard Urotherapy

Standard urotherapy is a first step in most cases of non-neurogenic daytime voiding disorders. It includes the following:

- Education regarding the function of the bladder and sphincter mechanism (information and demystification)
- Instructions on proper voiding position
- Instructions on a voiding regimen promoting regular voiding habits
- Lifestyle advice (e.g., fluid intake, constipation)
- Bladder diaries
- Support and encouragement
- Treatment of UTI, and antibiotic prophylaxis in children with recurrent infections

The first step is a dialogue between the child and the therapist about normal bladder function and about the child's problem. The child needs to understand what has to be corrected to be free from the problem. It is important to present this information from the individual patient's point of view, and to make it interesting and reliable.

To be able to empty the bladder completely, relaxation of the pelvic floor muscles needs to be practiced. The voiding position facilitates such relaxation. Sitting on the toilet, bent slightly forward with support for the thighs and feet, and legs slightly separated, is the optimal position to relax the pelvic floor muscles, according to a study by Wennergren and colleagues[21] performed in girls. A simple way to make a relaxed position clear to the child is to ask the child to sit on a chair or a toilet and try contracting versus relaxing, sitting on the edge of the seat, or in the position shown by Wennergren (Fig. 28-4). To be able to contract, the child can be encouraged to contract as if having a strong urge to void. When doing the opposite—relaxing—the child can feel the bottom falling down when sitting with support for the thighs and feet and slightly bent forward. These exercises can be used at home to find the right position. Conventional pelvic floor muscle exercise can also be used. To check the quality of the contraction, a finger on the perineal area can indicate if correct muscles are contracted.

To be able to develop voluntary control of voiding, the focus is the same as in toilet training, meaning initiating micturition rather than training to inhibit micturition. A timed voiding schedule should be constructed individually for each child to develop an appropriate filling/emptying balance of the bladder. Every second or third hour is usually suitable, but in severe cases of overactivity every hour can be necessary during the first few weeks. The schedule needs to be constructed with micturition intervals that prevent urgency from appearing, to stress voluntary initiation.

Depending on age, and with consideration of the child's situation in school, support is needed from parents and teachers. To avoid conflicts about responsibility in the parent-child relationship, the physician or therapist should ask the child how he or she would like to be reminded. Strategies are needed about who and when reminding will occur, and which predetermined voids the child himself or herself would like to be responsible for. An agreement needs to be reached about this strategy. Vibration alarm wristwatches can be useful, as can the alarm in cell phones. These can be used by the child or by the person doing the reminding.

Bladder diaries not only are mandatory for the initial assessment of voiding frequency, volumes, and number of incontinence episodes, but also as an instrument during the treatment period. The above-mentioned timed voiding should be performed including a logbook of the number and time of voiding and episodes of incontinence. The logbook is an instrument for recording the voiding regimen, but it can also be used as a pedagogic instrument in which the therapist and the child together can see how the child has succeeded, and what changes are needed for even better results. The time period for this initial treatment without additional therapies, such as anticholinergic medication, should not exceed 5 to 6 weeks, during which time one or two appointments should be scheduled for motivational discussions based on the diary. At these appointments, checks for residual urine and correction of emptying technique should be performed.

Lifestyle advice should always be given, and the appointments should be used to check compliance. Fluid intake has to be evenly spread during the awake hours, but not too close to bedtime.

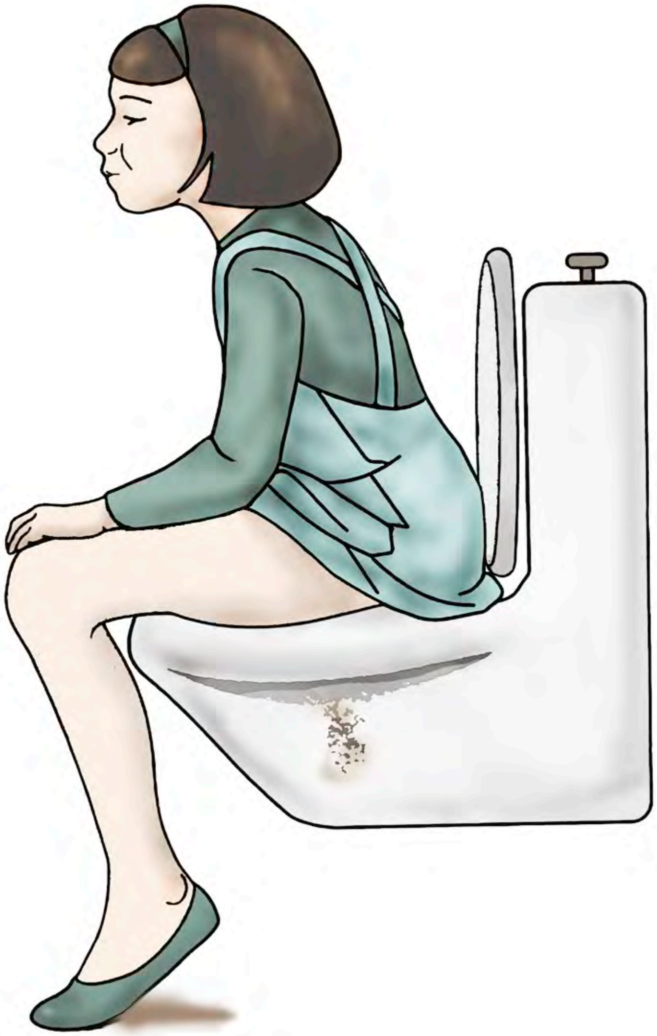


Figure 28-4 Optimal voiding position to relax the pelvic floor muscles. (Adapted from Wennergren HM, Öberg B, Sandstedt P. The importance of leg support for relaxation of the pelvic floor muscles: a surface electromyography study in healthy girls. *J Urol Nephrol.* 1991;25:205-213.)

Additional Therapies

BIOFEEDBACK

Biofeedback is often used in conjunction with a comprehensive rehabilitation program. It is a technique in which physiologic activity is conveyed to the patient as visual or acoustic signals, providing the patient with information about physiologic processes. Biofeedback may be used for the management of filling (detrusor overactivity) and voiding (dysfunctional voiding owing to pelvic floor muscle overactivity) phase abnormalities. In relation to the filling phase, it can help the child to recognize involuntary detrusor contractions, and in relation to the voiding phase, it can help the child to identify how to relax the pelvic floor muscles.

Biofeedback may be performed using a cystometrogram for children with involuntary detrusor contractions. In this situation, the child is taught how to recognize early and inhibit involuntary detrusor contractions, by watching the pressure curve during cystometry. When an involuntary contraction occurs, the child is encouraged to try consciously to suppress the contraction. This form of biofeedback is invasive and time-consuming and has limited use as routine treatment. To date, the outcome from such sessions has not been promising with regard to the long-term perspective.[22] If there is an indication for a cystometric investigation (e.g., in a patient with therapy-resistant urge syndrome), it can be used to teach the patient at the same time.

Biofeedback in the treatment of dysfunctional voiding is widely used and has been reported to be effective.[23] It is performed either by using uroflow only or in combination with pelvic floor electromyogram. The technique teaches the child how to relax the pelvic floor muscles during micturition: the child sits on a toilet with a flow transducer, watching the flow curve and the electromyogram online on a computer monitor, trying to empty completely in one relaxed continuous portion. Sometimes interactive computer games are used to make it more attractive to the child. Estimation of postvoid residual should always be checked after each voiding to see whether or not progress with the emptying ability is made.

NEUROMODULATION

Neuromodulation has been used in adults for various lower urinary tract symptoms. The invasive nature of the procedure (stimulation via anal or genital probe or via urethral catheter) makes it less attractive for children. Some studies report favorable effects in children, however. In OAB, stimulation of inhibitory pathways via an anal probe has been used,[24] and in the underactive bladder, the detrusor has been activated through intravesical stimulation.[25]

One technique that is easy to apply is transcutaneous electrical nerve stimulation with surface electrodes, aiming to stimulate the inhibitory nerves to the bladder via cutaneous stimulation over the sacral root (S3). Promising results have been shown in a few studies,[26] but no controlled studies are available. The technique has mainly been used in children in whom other treatment modalities have failed.

CLEAN INTERMITTENT SELF-CATHETERIZATION

In children with an underactive detrusor, bladder emptying can often be achieved with timed and double voiding. If this does not provide adequate results, clean intermittent self-catheterization may be tried. With devoted therapists, however, there is seldom any need for this technique in functional bladder disturbances.

The problem with clean intermittent self-catheterization in these functional disturbances is that we are dealing with children at ages where introduction of a catheter through the urethra, or just touching this area, can be very integrity-insulting. The problem in the long run is not that catheterization hurts, despite the fact that we are dealing with children with normal sensation levels, but coping with the situation; if friends hear about it they will be disgusted, and the child will be regarded as abnormal.[27] The acceptance and training period is often longer than for children with neuropathic bladder dysfunction, and support is needed during the treatment to handle problems that arise. Long-term compliance in these otherwise healthy children is also often lower.

Pharmacotherapy

Anticholinergic Drugs

Antimuscarinic therapy remains one of the more common forms of therapy for OAB. It is based on the concept that parasympathetic blockade of muscarinic receptors inhibits its activity in the bladder detrusor and is beneficial in the treatment of overactivity. Such agents have also been shown to increase bladder capacity, increase bladder compliance and decrease detrusor contractions in neurogenic detrusor overactivity, and play an important role in the treatment of these conditions.

In functional overactivity, pharmacotherapy is instituted when standard urotherapy does not suffice for a satisfactory outcome. Some physicians even use pharmacotherapy as the first-line treatment in children with daytime incontinence when bladder overactivity is suspected as the etiology. We do not support pharmacotherapy alone, but emphasize the importance of standard urotherapy together with the use of drugs. The unpredictable effects of these drugs on bladder overactivity may be due to some extent to the fact that good voiding habits are one of the factors needed for good results.

When anticholinergic drugs are used, there is always a risk of increase in postvoid residual, which should be checked at regular intervals, especially if the child suddenly presents with UTI, or notes a weaker urinary stream. Other common side effects include dry mouth, blurring of vision, constipation, and facial flushing. Occasionally, hyperpyrexia may occur, particularly when the child is exposed to the sun and hot weather. Central nervous system side effects have also been described, including irritation, aggressiveness, and hallucinations.

At present, the most widely used anticholinergic drug is oxybutynin hydrochloride, a tertiary amine. In addition to the anticholinergic effects, the agent has musculotropic relaxant effects and local anesthetic properties.[28] In the treatment of OAB, oxybutynin can be used in oral doses of 0.1 to 0.15 mg/kg twice daily. Efficacy of oxybutynin in OAB has been described in only a few open studies, and no placebo-controlled studies are available in children.[29]

Tolterodine is another, more recently developed anticholinergic drug mainly used for the treatment of OAB in adults. Several studies have been performed in children, and showed a satisfactory safety profile, so the drug is now used in many countries.[30] It has been described as "bladder selective," suggesting fewer anticholinergic side effects. The chemical nature of tolterodine makes it less likely to penetrate the blood-brain barrier. Trospium chloride and propiverine are other anticholinergics, but there are only a few inconsistent studies in children about their efficacy and tolerability.

α-Adrenergic Blocking Agents

Treatment of overactive pelvic floor and sphincter is much more difficult. The use of drugs with α-adrenergic blocking action seems promising in selected children with dysfunctional voiding and incomplete bladder emptying. Because no controlled prospective study using these drugs in children has been conducted, evidence of their usefulness to date is largely anecdotal.[31]

Botulinum Toxin

Botulinum toxin type A is currently used in children mainly with neurogenic detrusor overactivity, but has also been used for non-neurogenic OAB.[32] The initial results seem promising. In the study by Hoebeke and coworkers,[32] 100 IU were injected in the detrusor. The results lasted at least 12 months in most of the patients. Injection into the external sphincter is also possible in cases with pelvic floor overactivity. Results from a study with botulinum toxin type A in non-neurogenic conditions in children have been published more recently, with good but transient results.[33] The use of botulinum toxin type A in the non-neurogenic bladder regarding OAB and dysfunctional voiding has to be studied further before recommendations can be made about use in everyday practice because no placebo-controlled studies have been done.

Antibiotics

All children with symptomatic UTI require appropriate antibiotic therapy. If a child has an underlying voiding disorder associated with recurrent UTIs, prophylactic antibiotic therapy is recommended during the training period. Trimethoprim-sulfamethoxazole, nitrofurantoin, and trimethoprim alone have proven to be successful for antibiotic prophylaxis.

SPECIFIC CONDITIONS

The classification of the non-neurogenic daytime voiding disorders in Table 28-7 is according to the International Children's Continence Society Standardisation Committee document[34] and is in line with what is suggested in Chapter 27; for more information about the different conditions, see that chapter. With the noninvasive diagnostic tools discussed earlier, most of these conditions can be diagnosed to such an extent that treatment can be started without invasive diagnostic studies. In the case of no or poor response to the treatment, invasive diagnostic investigations might be warranted.

Overactive Bladder

The term *overactive bladder* is used to describe the symptom complex of urgency, with or without incontinence and frequent voiding (more than seven times a day), with overactive detrusor contractions during filling as the causative factor. In the history, holding maneuvers such as squatting, pressing the genitalia, or walking on tiptoes are commonly reported as a response to the urgency attacks, in an attempt to counteract leakage caused by the overactivity (Table 28-8). For children with incontinence, the problem becomes worse toward the end of the day, probably owing to loss of concentration and fatigue, and it may occur during the night. Children with this problem often diminish their fluid intake to minimize wetting.

Table 28-7 **Classification of Non-neuropathic Daytime Voiding Disorders**

Overactive bladder, urge incontinence
Voiding postponement
Underactive bladder
Dysfunctional voiding
Vaginal reflux
Giggle incontinence
Elimination syndrome
Non-neurogenic neurogenic bladder

A thorough history and a bladder diary show that these children experience urinary frequency, small voided volumes, and urgency incontinence, and their fluid intake is often low. With normal voiding and emptying of the bladder, indicated from the history and flow-residual study, no further investigations have to be made before treatment. The only exception is if the child has had recurrent UTIs together with bladder problems. In these cases, assessment with renal/bladder ultrasound should be performed and, depending on the age of the child, a VCUG to look for VUR.

Special attention has to be paid to the bowel history because the forceful contractions of the pelvic floor in response to the contractions during filling may lead to postponement of defecation. Constipation and fecal soiling are often found in children with OAB, and this condition has to be treated simultaneously.

Treatment in children with an urge syndrome should always start with the standard urotherapy treatment described earlier (Table 28-9). From the bladder diary the frequency of timed voiding should be determined together with the child, in such a way that urgency attacks are avoided. If voiding has to be more frequent than once every hour, there is a need for additional treatment with anticholinergic drugs. Such additional treatment is also indicated when no change is seen after 3 to 4 weeks of treatment.

Standard urotherapy treatment and anticholinergic drugs are the cornerstones in treatment of OAB. If this initial treatment fails, urodynamic studies are indicated. The main purpose is to exclude any other pathology, particularly neuropathic bladder dysfunction. The investigation can also be used for one-time education of the child, showing the unstable contractions during filling and the low volume and tower-shaped curve at voiding (biofeedback).

Another treatment modality in therapy-resistant cases of incontinence due to detrusor overactivity is neuromodulation. Transcutaneous electrical nerve stimulation can be tried because it is easy for the child and parent to do. More invasive

Table 28-8 **Symptoms and Findings in Overactive Bladder, Dysfunctional Voiding, and Voiding Postponement**

Symptoms	Overactive Bladder/Urge Syndrome	Dysfunctional Voiding	Voiding Postponement
Frequency	>7/day	Varying	<5/day
Urgency	Yes	Varying, decrease with age	Yes
Incontinence	With or without urge incontinence	Varying, decrease	Urge incontinence
Uroflowmetry	May be tower-shaped	Staccato/interrupted	Normal or staccato
Postvoid residual	Usually <20 mL	Increased (>20 mL)	Varying
Presenting symptoms	Frequency/urgency incontinence/holding maneuvers	Recurrent UTI/incontinence	Incontinence, holding maneuvers

UTI, urinary tract infection.

techniques with anal and genital stimulation should be used only in very selected cases. Biofeedback can also be used, preferably the cystometric technique. The invasiveness is a drawback, however, and biofeedback is seldom accepted by the child except in very difficult cases. For children who do not respond to any treatment, botulinum toxin type A injections in the detrusor muscle have been used, but these injections cannot yet be recommended as a standard treatment (see earlier discussion).

Children with OAB are often treated on an outpatient basis. The training is performed as self-care in daily life and under normal circumstances at home and school. There may be some difficulties in including the bladder regimen in an already full agenda, including factors beyond the control of the child. Benefits have been shown from treating these children as inpatients or at camps together with others who have similar problems.[35]

Few if any studies report on the results of the use of standard therapy only in OAB. Of the results available, signs and symptoms seems to disappear in about 50% of the children. If pharmacotherapy is added, the cure rate seems to increase to 70%.

Voiding Postponement

In voiding postponement, children postpone imminent micturition until overwhelmed by urgency, which makes them rush to the toilet, but often they are too late, and urge incontinence occurs. It has been suggested that the strong sphincter activity in voiding postponement is a behavioral maladjustment, and not a primary bladder/sphincter dysfunction.[8] Traditionally, this syndrome was thought to be an acquired disorder attributable to detrusor overactivity and caused by voluntary overactivity of the urethral sphincter until the bladder became filled.

A typical history includes urgency and incontinence with holding maneuvers, postponement of voiding, and quite a few micturitions per day (see Table 28-8). In the most benign cases, uroflow is often normal, and emptying is complete. In others, postvoid residual might be increased. No invasive investigations are recommended in the initial phase.

Treatment should start with standard urotherapy with the institution of a timed voiding schedule every 3 hours. Children are encouraged to go to the toilet even if they do not feel any need. This treatment is usually the only one needed for improvement.

Dysfunctional Voiding

Dysfunctional voiding refers to overactivity in the external sphincter or the pelvic floor during voiding, often with incomplete emptying as a result. The overactivity can be seen either as a *staccato* flow pattern caused by periodic bursts of pelvic floor activity during the voiding, resulting in dips in flow rate and coinciding with high bladder pressure, or as fractionated voiding with complete interruption of the urinary stream. This interruption is probably due to a weak detrusor contraction, which is easiest for the pelvic floor to overcome, and so the urine flow comes to a complete stop. To speed up micturition, these children often start to strain.

UTIs are common in these children, owing to incomplete voiding. Incontinence and straining at voiding are other common symptoms, as is constipation. The number of micturitions can be normal or infrequent. There can also be urgency owing to the fact that two out of three such children also show signs of overactivity, although in these cases it is easily inhibited (see Table 28-8).

Dysfunctional voiding can be suspected from the history and bladder diary, but uroflow is needed for diagnosis. Postvoid residual is often increased. In patients with dysfunctional voiding and a history of UTI, ultrasound of the kidneys and upper urinary tract is needed, and probably invasive studies to find out if VUR and renal damage are present. Urodynamic investigation is also often indicated, especially if there is poor emptying, and if the bladder problems are secondary in nature—in the first case to determine whether the bladder is hypocontractile and in the second to look for a neuropathic origin of the dysfunction.

As in other functional disturbances, treatment should start with standard urotherapy, treatment of constipation, and antibiotic prophylaxis if there are recurrent UTIs (Table 28-10). In children with decreased daytime micturition frequency (four or fewer), the number of micturitions should be increased to timed voiding once every third hour. Basic relaxed voiding training is often insufficient to help these children keep their pelvic floor relaxed during voiding. Treatment must be aimed at inducing full relaxation of the sphincter during voiding, with no residual urine. Strategies to achieve these goals include pelvic floor muscle awareness and timing training, repeated sessions of biofeedback visualization of pelvic floor activity, and relaxation. When large postvoid residuals are present, especially when in combination with recurrent infections, VUR, or renal damage, clean intermittent self-catheterization can be indicated. In these cases, drugs with α-blocking effects can also be an appropriate alternative before clean intermittent self-catheterization is introduced.

Treatment efficacy can be evaluated in terms of improvement of bladder emptying and resolution of associated symptoms. Although some studies have evaluated the effects of the above-discussed treatment modalities in patients with dysfunctional voiding, only one was randomized.[36] From the studies available, it seems that standard therapy alone has a cure rate of approximately 50% of patients with dysfunctional voiding. With addition of biofeedback, the cure rate would probably increase to 60% to 70%.

Table 28-9 **Treatment of Overactive Bladder**

Treat constipation
Prophylactic antibiotics if recurrent UTI
Urotherapy standard treatment
Anticholinergic drugs
(Neuromodulation, biofeedback, Botox injection in detrusor)

UTI, urinary tract infection.

Table 28-10 **Treatment of Dysfunctional Voiding**

Treat constipation
Prophylactic antibiotics if recurrent UTI
Urotherapy standard treatment
Flow-EMG biofeedback
(α-adrenergic blocking drugs, Botox injection in sphincter)

EMG, electromyogram; UTI, urinary tract infection.

Table 28-11 **Differential Diagnosis of Functional Non-neuropathic Daytime Disorders**

Ectopic ureter in girls
Urethral obstruction (e.g., posterior urethral valve)
Urethral frequency (e.g., urethritis)
Bladder retention (e.g., extravesical tumors, trauma, surgery)
Sexual abuse
Neurogenic bladder dysfunction owing to occult spinal dysraphism

Underactive Detrusor

The previous term for the rarely seen condition of underactive detrusor was *lazy bladder*. It is considered to be the result of dysfunctional voiding, but there are no data that support this. A child can qualify for the diagnosis only after examination with invasive urodynamics, to prove that detrusor activity is more or less absent during voiding, detrusor activity is driven by straining, and bladder capacity is high. The symptoms are low voiding frequency, straining and intermittent flow at voiding, recurrent UTI, incontinence, and often constipation.

Treatment of these children is aimed at improving bladder emptying, and clean intermittent self-catheterization is the procedure of choice. Intravesical electrostimulation has been described, but it is not yet recommended as a routine procedure for children.[20]

Non-neurogenic Neurogenic Bladder

Hinman and colleagues[37] first described non-neurogenic neurogenic bladder. A psychogenic model was initially adopted, but it has since been postulated that non-neurogenic neurogenic bladder is an extreme variant of dysfunctional voiding with demonstrable lower and upper tract deterioration mimicking that seen in children with neuropathic bladders. The history includes symptoms similar to those with dysfunctional voiding: daytime and nighttime incontinence, recurrent UTIs, and constipation.

The severity of the condition is first recognized after ultrasound of the upper and lower urinary tracts, which typically shows hydroureteronephrosis. In these cases, renal scintigraphy, VCUG, and urodynamics are indicated. VCUG typically shows a grossly trabeculated bladder, and VUR is seen in half of patients.[38] Half of the patients have renal damage. Urodynamics mimics the neurogenic bladder.[38] A neurogenic origin of the condition must be ruled out by MRI of the spinal cord.

The management of non-neurogenic neurogenic bladder depends on the severity of upper tract changes, but should be similar to the regimen for neurogenic bladder dysfunction. With upper tract changes, clean intermittent self-catheterization and antimuscarinic drugs should be the first-line treatment. If the patient is noncompliant with clean intermittent self-catheterization because of urethral discomfort, alternative access with a Mitrofanoff continent stoma may be obtained. Temporary urinary diversion or augmentation cystoplasty may be necessary.

Elimination Syndrome

The term *elimination syndrome* is used to designate non-neurogenic voiding disturbances seen together with bowel dysfunction (i.e., when there is a dysfunction of emptying of both systems). The common neural pathways and the mutual passage through the pelvic floor musculature may provide a theoretical basis for this relationship. Overactivity and cocontraction in the urethral and anal sphincter is considered causative, meaning that a functional obstruction is generated in both systems. It is more often seen in girls and is associated with recurrent UTI and VUR.[39] Assessment follows the same procedure as for other types of bladder dysfunction, with the addition of a bowel diary.

Treatment often begins with treatment of the bowel because there is evidence that amelioration of underlying constipation can relieve bladder symptoms. When stools are being passed regularly, treatment focuses on bladder training using the methods discussed earlier for dysfunctional voiding. Pelvic floor awareness and biofeedback therapy are often important parts of treatment.

Detrusor-Sphincter Dysfunction, Recurrent Urinary Tract Infection, and Vesicoureteral Reflux

Vaginal Reflux

Toilet-trained prepubertal girls who experience moderate incontinence consistently occurring within 10 minutes after normal voiding are said to have vaginal reflux if no underlying mechanism other than vaginal entrapment of urine is obvious. The condition is not associated with other lower urinary tract symptoms. It may be due to labial adhesions or an inappropriate position on the toilet. The classic presentation is that of a girl who does not spread her legs enough during voiding and who is not sitting bent forward and all the way back on the toilet seat. The treatment is often simple: instructions about changes in the voiding position with a recommendation of widely abducted legs and while wiping oneself to press upward to empty the vagina completely. If there are labial adhesions, these should be treated.

Giggle Incontinence

In some children, giggling can trigger partial or complete bladder emptying well into their teenage years and sometimes into adulthood.[40] Typically, the patient does not experience any other lower urinary tract symptoms, such as incontinence during the day or night. The etiology is unknown, but it has been suggested that laughter triggers the micturition reflex via central mechanisms in such a way that the central inhibition is blocked.

No simple treatment is available. One way to describe the problem is as OAB triggered by giggling. Standard therapy can be useful together with pelvic floor muscle exercises to strengthen awareness of the muscles, to provide an emergency brake. Central nervous system stimulatory drugs, such as methylphenidate, have been reported to have good effects. Treatment with central nervous system–stimulating drugs should be done very selectively, however, because of the addictive nature of these drugs.[41]

DIFFERENTIAL DIAGNOSIS OF NON-NEUROGENIC VOIDING DYSFUNCTION

There are many differential diagnoses for non-neurogenic voiding dysfunction, the most common of which are listed in Table 28-11.

Ectopic Ureter in Girls

In girls, an ectopic ureter draining into the distal urethra or vaginal introitus may result in continuous leakage of urine, but with normal voids and no other lower urinary tract symptoms. A pad test is the best way to establish that the incontinence is continuous.

The ectopic ureter is most often combined with a duplex kidney and associated with upper pole moiety. Diagnosis can be suspected on the basis of an ultrasound, but intravenous urography is the diagnostic tool if the moiety is functional. If it is nonfunctional, computed tomography (CT) or MRI is recommended for diagnosis. Renal scans (dimercaptosuccinic acid [DMSA] or mercaptoacetyltriglycerine [MAG3]) are also useful because even poorly functioning moieties can often be detected. Treatment is surgical, with removal of a poorly functioning upper pool moiety (heminephrectomy) or implantation of the ectopic ureter in the bladder if the function is good in the corresponding part of the kidney.

Urethral Obstruction

In a boy with daytime voiding problems in whom uroflowmetry shows an obstructive flow curve in repeated assessments, VCUG should be performed to rule out an anatomic obstruction in the urethra, such as posterior urethral valve, strictures, and syringocele.

Daytime Frequency Syndrome

Daytime frequency syndrome is seen most often in boys 4 to 8 years old, but may occur in either sex at any age beyond toilet training. Onset is acute and cannot be attributed to any physical problem. Children with this problem urinate multiple times per hour, have no incontinence, and often get out of bed several times before falling asleep, but then sleep through the night. No evaluations except for urine culture are necessary. The condition is self-limiting.

Urinary Retention

Urinary retention in sometimes seen in children, often younger than 4 or 5 years old, who void infrequently, usually in combination with voiding postponement and constipation. Important structural differential diagnoses may explain the retention, however, indicating prostatic rhabdomyosarcoma and other expansive processes in the pelvis. For this reason, all children with true urinary retention should be assessed with ultrasound of the bladder and the pelvic area to exclude expansive processes. Treatment of a child with functional retention should be a timed voiding regimen, even if the child is younger than 5. In these cases, the parents have to be responsible for compliance.

Sexual Abuse

Sexual abuse is defined as imposed sexual activity. Some have suggested that 25% of girls and 10% of boys have been sexually abused before age 16.[42] Often there is a sudden change in behavior. Regression can be seen in preschool children with development of enuresis; they start to suck their thumbs, use baby talk, and are afraid of sleeping alone. In school-age children, signs such as sleep difficulties, phobias, and acting out sexually are seen. The most common symptoms are psychosomatic complaints, such as voiding problems, headache, and stomachache. History taking is important in these cases.

Clinicians who evaluate voiding disorders must always bear the possibility of sexual abuse in mind as an underlying cause of secondary voiding dysfunction, particularly in older children. A question about sexual abuse can be included in a structured voiding history. Asking does not mean suspecting. Because the media is very attentive to stories about sexual abuse, parents can understand why you are asking. In the physical examination situation, there can be a question about other physical examinations of the child or touching of the genitalia. One can expect a prompt answer, but the question may also provoke thoughts. If sexual abuse is suspected, there are standards regarding how to handle the situation.

Epispadias in Girls

Continuous leakage of urine in a girl may be attributable to isolated epispadias anomaly. This diagnosis can often be made with a thorough examination of the region of the urethral meatus.

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CHAPTER 29

NOCTURNAL ENURESIS

Tryggve Nevéus and Arne Stenberg

Although bed-wetting, or enuresis, is a very common disorder, treatment success is still far from impressive. One of the main reasons for this is that enuresis research until the last decades has been almost exclusively psychiatrically focused, causing old misconceptions to linger and new ones to arise. This situation has changed for the better as urodynamic, endocrinologic, and neurologic factors have been shown to be pathogenically important, and treatment modalities with proven efficacy have been developed. It has been shown that psychological problems in enuretic children most often are the consequences, not the causes, of the bed-wetting. Many health professionals confronted with enuretic children tell the families that bed-wetting is trivial and need not be treated, or implicate behavioral, social, or psychological causes as the root of the problem. Enuresis is trivial only if the child and the family regard it as trivial; otherwise, it should certainly be treated.

DEFINITIONS

According to the new International Children's Continence Society guidelines for lower urinary tract terminology,[1] which are consistently adhered to in this chapter, *enuresis* is synonymous to *nocturnal incontinence* and means involuntary voiding while asleep in a child 5 years old or older. Bed-wetting is called enuresis (or nocturnal enuresis for clarity) regardless of whether the voids are complete and urologically normal or not, and regardless of whether or not the child also has daytime incontinence. The only kind of bed-wetting that is not included in the term is the continuous incontinence affecting children with urogenital malformations or iatrogenic sphincter damage.

Secondary enuresis denotes bed-wetting in a child who has previously been dry for at least 6 months, whereas *primary enuresis* denotes that no such intervening period of dryness has occurred. Enuresis without any other concomitant lower urinary tract symptoms, such as daytime incontinence, urgency, or interrupted stream, is called *monosymptomatic enuresis*. According to earlier terminology, monosymptomatic enuresis denoted only enuresis without daytime incontinence. In accordance with the International Children's Continence Society and International Continence Society guidelines, we use the term *voided volumes* instead of *bladder capacity* when discussing bladder volumes.

EPIDEMIOLOGY

Enuresis is a common condition. If a wetting frequency of at least one "wet night" per month is taken into account, the prevalence is probably greater than 10% among 6-year-olds,[2] around 5% among 10-year-olds,[3,4] and 0.5% to 1% among teenagers and young adults.[5] The natural history of enuresis is difficult to assess, but a spontaneous cure rate of 15% per year is often quoted.[6]

Enuresis without daytime incontinence is 1.5 to 2 times more common in boys than girls.[2,3,7] In children with combined daytime and nighttime wetting and in adults, no such gender differences are found.[2,3,5] Daytime incontinence is more common in girls.[2,3]

GENETICS

Enuresis has long been known to be strongly influenced by hereditary factors, as shown by twin studies[8] and numerous epidemiologic surveys.[3,9-13] The recurrence risk for a child to be affected by enuresis is 40% if one parent and 70% if both parents had been enuretic.[14] Several different "enuresis genes" have been found.[15] In a more recent study on a large group of children with different kinds of enuresis (i.e., monosymptomatic nocturnal enuresis, combined enuresis and incontinence, primary enuresis, and secondary enuresis), it was found, however, that there was no clear correspondence between phenotype (subtype of enuresis) and genotype.[16]

PATHOGENESIS

Nocturnal Polyuria

The discovery that many enuretic children have an exaggerated nocturnal urine production has justly been considered the starting point of modern enuresis research. It was shown that this group of children lacked the physiologic nocturnal peak of the antidiuretic neurohypophyseal hormone vasopressin secretion, and consequently had a nocturnal urine production exceeding the amount that their bladders could hold.[17,18] This finding has since been repeated[19-21] *and* contradicted.[22-25] A contributing explanation for the conflicting results could be the fact that vasopressin is released in a pulsatile fashion,[26] and accurate assessment of circadian profiles would call for measurements every 15 minutes or so. It has also been shown that the polyuria of some enuretic children is not caused by vasopressin deficiency.[21,27]

Another problem with the polyuria hypothesis is the finding that nocturnal polyuria is not a phenomenon exclusive to bed wetters. It has been shown that approximately 10% of dry children produce more urine during the night than during the day.[28] The fact that nocturia is a common phenomenon among dry children[3,7] indicates that nocturnal polyuria may be common as well.

Even with these objections taken in consideration, it is generally agreed that nocturnal polyuria is common among enuretic children, and that vasopressin deficiency may be causing this polyuria at least in some of them. All bed-wetting children do not have polyuria, however. The polyuria hypothesis does not explain why the children do not wake up to void.

Detrusor Overactivity

Because of the great overlap between the groups of bed-wetting and daytime incontinent children,[2,3,5,7,10] and the prominent role of detrusor overactivity in the pathogenesis of the latter condition, detrusor overactivity has been implicated as a pathogenic factor in nocturnal enuresis as well. Sleep cystometries in enuretic children have revealed that some of them exhibit frequent uninhibited detrusor contractions at night, although the bladder was stable during the daytime hours.[29,30] In studies in which subjects with combined daytime and nighttime wetting were included, the finding of urodynamic abnormalities was even more common.[31,32] In a cystometric study in a group of children with therapy-resistant enuresis—without daytime incontinence—*all* children examined were found to exhibit pathologic cystometrograms during sleep, with nocturnal detrusor overactivity, dysfunctional voids, or obstruction, or some combination.[33]

An overactive bladder is usually a small bladder. It has been noted for several decades that enuretic children tend to void in smaller portions than dry children,[33-36] and they go to the toilet more often.[37,38] Urgency—the subjective sign of detrusor overactivity—is more commonly experienced in this group.[3] It has been shown that enuresis sometimes can be successfully treated with anticholinergic or smooth muscle relaxant drugs.[39] All these considerations make it reasonable to conclude that there is a subgroup of enuretic children in which nocturnal detrusor overactivity is a pathogenetic factor behind their enuresis.

There is an association between constipation and detrusor overactivity.[40] Constipation and encopresis are common among children with incontinence,[41-43] and these children often become dry when treated for constipation.[43,44] The mechanism behind this association is probably that the bowel may compress the bladder, making it more prone to contraction,[45] and that the frequent and forceful contractions of the pelvic floor that occur in detrusor hyperactivity cause constipation.

Impaired Arousal Mechanisms

The idea that enuretic children are "deep sleepers" is not new.[46] Subjectively low arousability has been reported in numerous epidemiologic studies.[31,42,47-49] The observation by parents of children being treated with the enuresis alarm that the alarm wakes everyone in the house *except* the child who is using it is also well known. This observation involves a "control group" (i.e., the rest of the family) as well.

Studies on objective arousal thresholds of enuretic children are more problematic because the recording of sleep electroencephalograms gives no information regarding differences in arousability among subjects. The fact that the sleep electroencephalogram of enuretic children is not clearly different from that of non–bed wetters[50] has often led to the erroneous conclusion that enuretic children do not sleep more "deeply" than their dry peers. In the elegant study by Wolfish and coworkers,[51] it could be clearly shown, however, that children with severe enuresis were significantly more difficult to arouse from sleep than controls. Note the semantic confusion here: Maybe we should not say that bed wetters sleep more deeply—their quality of sleep is not electroencephalographically more "deep" than that of other children—but that they are more difficult to arouse completely from sleep, which they are.

Bladder distention and detrusor contractions are recognized as strong arousal stimuli.[52,53] It is logical for sleep to play at least a permissive role in the pathogenesis of enuresis because neither bladder overfilling nor detrusor contractions would fail to arouse a person with normal arousal mechanisms.

Enuresis and Psychiatry

The old opinion that enuresis mainly is a psychiatric disorder[54] is now obsolete because the behavior problems among enuretic children that would be expected from psychiatric explanation models have not been found,[55,56] no differences regarding stressful family events or toilet training have been detected,[57,58] and the prevalence of enuresis has not been found to differ between children with and without psychosocial problems.[59] Psychotherapy has not been shown to be superior to somatically oriented enuresis treatment, and there is no tendency for symptom substitution among bed wetters who become dry.[60]

There is, however, a certain psychiatric comorbidity in children with wetting problems, a comorbidity that is most pronounced in children with daytime incontinence or secondary enuresis.[61,62] Children with primary nocturnal enuresis without concomitant daytime incontinence do not differ from the normal population in these respects.[62]

It would probably be too far to conclude that psychological or psychiatric factors have no importance in enuresis. Bed-wetting is a social stigma and a heavy burden for a growing child. Enuretic children have low self-esteem compared with dry children, and this difference disappears when the children become dry.[63] Many of the psychiatric or psychological abnormalities attributed to enuretic children in the past are probably consequences of the bed-wetting instead of causes.

Another link between enuresis and psychiatry is the definite overrepresentation of bed wetters among children with attention-deficit/hyperactivity disorder or related neuropsychiatric conditions.[64,65] Although this association is not just coincidental, it is unclear if the enuresis/incontinence is caused by the neuropsychiatric disturbance, or if the two conditions have a common neurologic background; the latter explanation is the more plausible.

There have been anecdotal reports about enuresis in children who have been the victims of sexual abuse,[66] but there is no evidence that the one should have caused the other. The association with later daytime incontinence and other lower urinary tract malfunction is more substantiated.[67] Although sexual abuse occurs in all social groups and family constellations, the fact that a child is a bed wetter should not in itself constitute a reason to suspect that he or she has been sexually abused.

Pathogenic Subtypes of Enuresis

From the aforementioned considerations, it should be evident that enuresis is a clinically and pathogenetically heterogeneous disorder. Different groups of bed-wetting children have different underlying defects and require different treatments to become dry.

It has been convincingly shown that nocturnal polyuria is characteristic of children with enuresis that responds favorably to antidiuretic treatment.[19,25,36,68,69] These children may show signs of defective renal concentrating ability,[36] their voided volumes are usually in the normal range,[36] and they are not more prone to urgency symptoms than the general population. We have chosen to call this subtype of enuresis *diuresis-dependent enuresis*. These children wet their beds because of bladder overfilling, and because they sleep too deeply to wake up when the bladder is full.

Nonresponders to antidiuretic therapy can be suspected to have detrusor overactivity because they tend to have smaller voided volumes[36,70-72] and may respond favorably to anticholinergic treatment.[39] This suspicion has been cystometrically supported.[33] We use the term *detrusor-dependent enuresis* to denote this subgroup. These children wet their beds because of micturition contractions that are not inhibited and that fail to awaken them from sleep. Many of these children have daytime symptoms (urgency or incontinence or both) of varying degree as well, or are constipated,[40] but their nocturnal urine output and renal concentration capacity are normal.[36] Some children exhibit signs of both diuresis and detrusor dependency, such

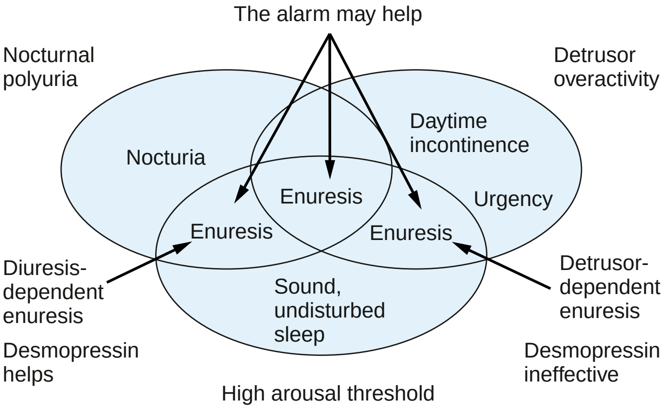

Figure 29-1 Pathogenic subtypes of enuresis.

as children who become dry only with combined anticholinergic and antidiuretic therapy. The pathogenic and clinical subdivisions of enuresis are shown graphically in Figure 29-1.

Enuresis Secondary to Other Disorders

Children with diabetes mellitus may have enuresis as a presenting symptom, although most do not.[73] Likewise, polyuria resulting from diabetes insipidus (nephrogenic or central) or polyuric renal failure (i.e., boys with urethral valves) may cause enuresis as well. These children are very thirsty and usually need to get up at night to drink. Urinary tract infection may cause a previously dry child to start wetting, but this incontinence is usually not confined to the night, and in most cases, additional symptoms, such as dysuria, are present. A few enuretic children have heavy snoring and sleep apneas owing to enlarged tonsils or nasal polyps, and become dry when the upper airway obstruction has been removed.[74] The enuresis of these children could be explained by paradoxical low arousability (because of continuous arousal stimuli from the upper airways), nocturnal polyuria, or a combination of the two.[75]

INITIAL EVALUATION

The primary evaluation of an enuretic child is simple and straightforward, but it is time-consuming because assessment and diagnosis are based on history data. Also, treatment success depends to significant degree on establishing a good patient-physician relationship. The initial evaluation requires at least half an hour.

The history is heavily focused on micturition habits. “How often is the bed wet?” “Has it always been this way?” “Do you wet your underwear during the day as well, or has that been the problem earlier?” It is paramount to differentiate children with secondary enuresis from children who have never been reliably dry at night because the few bed wetters with kidney disease or diabetes as an underlying cause usually belong to the former group. For the same reason, questions should be asked about the child’s general health and the child’s drinking behavior. Children with excessive thirst and a need to get up and drink at night may have decreased renal concentration capacity. Urgency symptoms and signs of urinary tract infection (e.g., dysuria) should be sought, and also symptoms suggesting constipation, such as encopresis, infrequent bowel movements, or the passage of hard stools.

Parents should be asked about enuresis in other family members, and about the arousability of the child at night. Although almost all bed wetters are perceived as “deep sleepers” by their parents, children who are difficult to communicate with even when they have been forcefully awakened at night may not be ideal candidates for the alarm treatment (see later). It is also important to find out whether the child regards the enuresis as a serious problem, and if it affects his or her life greatly. A penetrating psychiatric evaluation is not needed if the child does not exhibit overt signs of psychiatric disease or serious social maladjustment.

The physical examination should include inspection of the genitals and a standard neurologic examination. A rectal examination should be performed if constipation is suspected because the presence of stool in the rectum (without the child sensing a need to go to the toilet) is strongly indicative of fecal impaction.[76]

Blood samples or other invasive investigations are not needed at this stage (and seldom later) if the case history and physical examination does not indicate underlying kidney disease or urologic abnormality. Ultrasound or other radiologic evaluations are not informative. Even the need for urinalyses can be questioned if the child has never been reliably dry because it would be strange for bed-wetting to be the sole manifestation of diabetes mellitus or urinary tract infection for several years. In secondary enuresis, however, urinalyses are needed, and when there is concomitant daytime incontinence or dysuria as well.

Child with Combined Enuresis and Daytime Incontinence

Although the traditional view that enuresis cannot be successfully treated before the child has become dry during the day has been challenged more recently,[77] it is still reasonable to deal with the daytime problem first in children with both conditions. The reason is that daytime incontinence is more socially disturbing for the child and may signal an underlying bladder disturbance associated with the risk for urinary tract infections.

Bladder training is started, preferably with the help of a urotherapist. Pharmacologic treatment with anticholinergics may be indicated if bladder training alone does not succeed. Urodynamic investigations may also be needed in these children, but seldom at this early stage, unless there are symptoms or signs suggesting outlet obstruction (i.e., weak urinary stream), aberrant ureter (i.e., continuous leakage), or other urologic conditions requiring specific treatment. The presence of residual urine must be ruled out before anticholinergic treatment can be started.

INITIAL TREATMENT

When organic disease is not suspected, daytime incontinence is not an issue, and the child has nocturnal enuresis that he or she considers a significant problem (usually by approximately age 6 years), it should be treated. Although success has been claimed for numerous drugs and nonpharmacologic therapies, only a few of them have stood the test of controlled trials. Only the enuresis alarm and desmopressin can presently be recommended as first-line therapies. Initial treatment usually is with one of these, and our recommendation is to leave this choice to the child and family.

General Advice

Regardless of whether the alarm or desmopressin is the first choice, the family needs to be informed about simple measures that can be undertaken to facilitate the process of becoming dry. Most families have already tried, without success, to make their child dry by restricting fluid intake in the evenings. Often a better strategy is to ensure that the child drinks enough during the daytime because many children with disturbed bladder function tend to drink very little and become thirsty as the day progresses. Extra glasses of water at breakfast and lunch are often a good idea, and then the child can be allowed to drink in the evening if he or she is thirsty.

Sound, regular micturition habits should be instituted, especially in children who have non-monosymptomatic enuresis. This means that the child should void approximately six times per day with a maximum interval of 3 hours. Diapers should not be used unless the *child* wants to use them. Parents who regularly wake the child at night to take him or her to the toilet should be informed that this practice is neither medically indicated (the child will not get urinary tract infections from sleeping in a wet pajamas) nor useful as an antienuretic therapy (if it helps, it will help only for that specific night).

Psychological Aspects

Although most parents nowadays do not reproach or punish their bed-wetting children, many children nevertheless think that bed-wetting is “their own fault.” One of the duties of health care professionals is to tell the child that this is not the case. We usually tell the child that “you wet your bed because your bladder is not as smart as you are,” or “the reason that you pee in your bed is that your kidneys make too much pee during the night.” Another common problem is that the child thinks that he or she is (almost) the only bed-wetting person in the world. This misconception is strengthened by the fact that most bed-wetting children keep their problem top secret even from their closest friends. This dark secret can make the child terribly lonely. Some children even report that because of that eternal hidden knowledge, they can never feel really happy. Consequently, the physician should inform the child that enuresis is a very common disorder, and that it can be successfully treated. A good piece of advice to these children is that they tell their best friends about their problem; this usually—in contrast to the child’s belief—does not result in teasing and bullying, and it lessens the child’s sense of loneliness.

Enuresis Alarm

The principle behind the enuresis alarm is deceivingly simple: By waking the child from sleep at the moment of enuresis, he or she gradually learns to recognize the imminent bladder voiding, and either suppresses the detrusor contraction or wakes up and goes to the toilet. Although it has been questioned whether we can really be taught anything while we sleep, the fact remains that the alarm works—success rate is around 60% to 70%,[78,79] and can be even higher in well-motivated and well-informed families. Although 5% to 30% of children may relapse after treatment,[78,80] it can still be considered the only truly curative method.

The apparatus consists of a urine detector—placed either in the child’s underclothes or beneath the sheets—that is connected to an alarm that emits a strong wake-up signal when the detector is activated. The advantages of the alarm treatment are that it has a definite curative potential, and that it is completely harmless. It does require a high degree of compliance and motivation, however, from the parents and the child to be effective. Children with infrequent wetting episodes are not suitable candidates. Children whose parents show signs of intolerance toward the child’s bed-wetting also are unsuitable candidates.

Families using this treatment should be instructed to help the child to awaken and go to the toilet immediately when the alarm sounds. Often in the beginning of the treatment, the child does not awake by himself or herself at the sound of the alarm. This usually means that one parent should sleep in the same room as the child. It is imperative that the treatment be continuous; no interruptions during weekends should be allowed. The child (and the rest of the family) should not be awakened more than once per night, however, because too much sleep disruption could impair daytime alertness. Treatment should be continued until either 14 consecutive dry nights have been achieved or more than 6 weeks have passed without signs of effect. Children relapsing after successful alarm treatment usually can easily be treated with a second alarm session.

Desmopressin

Desmopressin is a synthetic analogue of vasopressin, devoid of pressor effects but with intact antidiuretic action.[81] Since the late 1970s, many studies have shown that the drug is useful against enuresis.[48,78,82-91] Reported success rates have ranged from 40% to 80%, but relapse after treatment cessation is the rule.[85,88] The mechanism of action is probably that the time of bladder (over-) filling is delayed until the morning, although this explanation has been questioned.[92] Treatment with desmopressin can be considered safe, and side effects are exceedingly rare,[93] but if the drug is combined with excessive fluid intake, there is a significant risk of hyponatremia with convulsions or unconsciousness.[94]

The advantages of desmopressin, apart from the lack of toxicity, are that it is easy to administer, and effects appear without delay. The major drawbacks are the low curative potential and the cost. The usual dose is 0.2 to 0.4 mg orally, or 120 to 240 μg with the quick-melting oral lyophilisate tablets, or 20 to 40 μg intranasally at bedtime. When prescribing desmopressin, the physician must tell the family that large amounts of liquid should not be consumed on nights when the drug is taken. One practical approach is to allow one glass to drink at dinner and half a glass at bedtime.

Because the response or nonresponse to this drug is evident without delay, there is no reason to treat for more than 2 weeks if the child experiences no beneficial effects of the drug. For treatment responders, the decision to take medication continuously or just on “important” nights should be left to the families. If the child chooses the former strategy, a 1-week interruption is recommended every 3 months to see if the problem has disappeared and treatment is no longer necessary.

EVALUATION OF THERAPY-RESISTANT CHILDREN

Children with enuresis that responds neither to the alarm nor to desmopressin in ordinary dosage, and nonresponders to desmopressin in whom the alarm is considered unsuitable for psychosocial causes, should be referred to a specialist, usually a pediatric urologist or a pediatrician. These children usually have detrusor-dependent enuresis, with daytime symptoms such as urgency, voiding postponement, or increased or decreased voiding frequency, and many are constipated as well. In our experience, many of these therapy-resistant children have neuropsychiatric comorbidity.

The urodynamic and renal status of therapy-resistant children should be evaluated with extra care. All these children should be asked to complete a home *bladder diary*. A good bladder diary should include the time and volume for every micturition, fluid intake over 2 to 3 days, and documentation of wetting accidents, and bowel movements for at least 1 week. This diary provides indispensable information regarding bladder and bowel function. *Uroflowmetry measurements* are performed to detect signs of outlet obstruction or detrusor underactivity, and residual urine is assessed with a simple ultrasound examination. Morning urine osmolality should be tested in children who exhibit excessive fluid intake, but is not otherwise necessary. If osmolality is repeatedly found to be low (<500 mOsm/kg), an inpatient thirst provocation test may be indicated to assess renal concentration capacity.

Cystometry, cystoscopy, and radiologic evaluation of the kidneys and urinary tract are unnecessary, provided that the above-mentioned examinations do not reveal signs of neurogenic bladder disturbances, renal damage, or bladder outlet obstruction. Blood tests do not give much useful information if there are no indications of kidney disease.

In many cases, nonresponse to the enuresis alarm may simply be due to the family not having been properly instructed. The parents may not have been informed that their child may be unable to wake up by himself or herself at the start of treatment, or the treatment may have been interrupted. A new treatment session after proper information may solve the problem. If a long time has elapsed since the last alarm treatment, a new try might have greater success because the child may now be more easily awakened at night, or the family may be more motivated. We recommend a new alarm treatment session every second year or so.

Constipation should always be kept in mind in children with therapy-resistant enuresis, especially if they also have encopresis. Some constipated children defecate every day and have no definite bowel complaints. The diagnosis of constipation is not difficult to ascertain, however, if bowel movements are included in the bladder diary, and a manual rectal examination is performed. Treatment of these children should be aimed at the bowel first: (1) enemas; (2) laxatives; and (3) institution of regular, daily bowel habits.

SECOND-LINE TREATMENT MODALITIES

Urotherapy

Standard urotherapy involves the following basic components: (1) explanation about normal bladder function and in what way the particular child deviates from normal; (2) instruction about sound, regular voiding habits and proper fluid intake (see earlier); (3) recording of symptoms and micturition behavior, using repeated bladder diaries; and (4) follow-up and support. Urotherapy is the mainstay in the treatment of daytime incontinence, and a few studies indicate that it may help children with isolated enuresis as well,[95-97] but proper randomized controlled studies in this indication are so far lacking.[98] Although this strategy is not harmful, and basic bladder advice should be a part of the treatment of every child with daytime or nighttime incontinence, in our experience urotherapy alone is seldom effective in the treatment of therapy-resistant nocturnal enuresis.

Anticholinergics

Foremost among parasympatholytic substances used in urologic practice is oxybutynin, a drug with anticholinergic and smooth muscle relaxant properties[99] that has proven to be effective in the treatment of daytime incontinence caused by detrusor overactivity.[100] Some investigators have treated enuresis with oxybutynin and have reported some success.[101-103] The success rate is greatest in children with combined daytime and nighttime wetting, in children with therapy-resistant enuresis,[39] and in children with proven detrusor overactivity.[104] In unselected children with monosymptomatic nocturnal enuresis, the benefit is less obvious,[105] but our experience is that many children in the therapy-resistant group (i.e., children with no response to desmopressin or the alarm) do become dry when treated with oxybutynin, especially when combined with desmopressin.[39]

The toxicity of oxybutynin is low,[106] but side effects (mainly dryness of the mouth, constipation, and mood changes) limit its usefulness.[107] Especially, constipation is a problem because children with detrusor overactivity, as mentioned earlier, are often constipated from the start, and the development of constipation may aggravate detrusor overactivity and counteract the beneficial effects of the drug. The use of anticholinergics may lead to the accumulation of residual urine and create a risk for urinary tract infection. The novel anticholinergic and smooth muscle relaxant drug tolterodine has shown a more favorable therapeutic profile, with the same clinical efficacy and a reduced frequency of side effects in children and adults,[108-113] but the same precautions still apply.

Given the lack of other treatment modalities, and the concerns about the cardiotoxicity of imipramine (see later), we consider anticholinergics to be the treatment of choice for therapy-resistant enuretic children, after constipation and concomitant daytime incontinence have been ruled out or treated. This treatment is experience-based, however, not evidence-based. Our practice is to give 1 to 4 mg of tolterodine in the evening. Medication is unnecessary in the morning if there is no concomitant daytime incontinence. Treatment success is estimated after approximately 2 months. If response is partial, the addition of desmopressin in standard dosage is often beneficial. An alternative strategy is to start with combined treatment and then remove the desmopressin component and see if monotherapy suffices. Anticholinergics should not be given if the child has significant residual urine measured after repeated voids.

In our experience, responders to anticholinergic therapy usually need to continue this medication for 6 to 12 months. During this treatment, the child should develop sound, regular voiding habits, and the family should watch out for signs of constipation or urinary tract infection.

A child who develops urinary tract infection during anticholinergic treatment should have residual urine measured and stop treatment, at least temporarily, until the infection has been treated, and residual urine has disappeared. Constipation during anticholinergic treatment is usually heralded by stomach pains, encopresis, or simply a gradually decreased treatment success. In these children, medication should be temporarily discontinued, and the constipation should be treated. Anticholinergic treatment can then be started afresh, while the child continues to take bulk laxatives.

Tricyclic Antidepressants

Since the early 1960s, imipramine has been successfully used in the treatment of enuresis.[114] Numerous studies, several of them placebo-controlled, have shown that about 50% of enuretic children are helped.[78,115-118] The antienuretic potential of imipramine is likely to reside in central noradrenergic facilitation, not in the anticholinergic side effects.[119] Side effects of imipramine treatment (e.g., nausea, anticholinergic side effects) are usually minor,[120] but the substance is potentially cardiotoxic, and even lethal reactions have been reported when the drug has been overdosed or given to individuals with unstable cardiac arrhythmias.[121] Another drawback is the fact that some children experience mood changes while taking the drug.

If desmopressin, alarm, and anticholinergic treatment all have been tried without success or have been judged unsuitable, the cautious use of imipramine is still warranted. This is, however, a matter for specialist clinics and not for the general pediatrician. If the drug is given, it is imperative that (1) the standard antienuretic dosage of 25 to 50 mg at bedtime is not exceeded; (2) the drug is not prescribed to children who have any heart complaints (e.g., palpitations, syncope episodes) or family history of unstable cardiac arrhythmias; and (3) the parents are made aware that the pills need to be kept safely locked.

Imipramine is helpful in approximately 50% of cases unresponsive to first-line and second-line treatment, and, as with anticholinergics, the success rate increases when the drug is combined with desmopressin.[119] If there is no effect after 1 month, the treatment should be discontinued. If the effect is good, there should still be regular medicine-free intervals because otherwise the risk for tolerance is great.

Concerns of cardiotoxicity and the decreased availability of imipramine have made us look for alternative but related treatments. We have used the noncardiotoxic central noradrenergic–acting antidepressant reboxetine in a group of severely therapy-resistant enuretic children. Results so far are encouraging, but do not allow for any recommendations.[122]

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CHAPTER 30

THE BLADDER EXSTROPHY–EPISPADIAS–CLOACAL EXSTROPHY COMPLEX

J. Todd Purves and John P. Gearhart

This chapter deals with the surgical management of classic bladder exstrophy, epispadias, and cloacal exstrophy, with an emphasis on the modern therapies for these conditions.

The primary objectives of the modern surgical management of classic bladder exstrophy are (1) a secure abdominal closure, (2) reconstruction of a functional and cosmetically acceptable penis in the male or female external genitalia in the female, and (3) urinary continence with the preservation of renal function. Currently, these objectives can best be achieved with newborn primary bladder and posterior urethral closure, early epispadias repair, and, finally, bladder neck reconstruction when the bladder reaches an appropriate volume for an outlet procedure. Occasionally, in very select patients, bladder closure and epispadias repair can be combined and bladder neck repair performed when an adequate capacity is reached and the child is ready to be dry.

Surgical reconstruction of cloacal exstrophy, the most severe variant of the exstrophy complex described, has improved with advances in pediatric anesthesia, neonatal care, and nutrition, along with the application of principles that have evolved in the treatment of classic bladder exstrophy, including the use of osteotomies in most patients.

BLADDER EXSTROPHY

Incidence and Inheritance

Data from the International Clearinghouse of Birth Defects Monitoring Systems[1] and the Healthcare Cost and Utilization Project Nationwide Inpatient Sample[2] estimate the incidence of bladder exstrophy to be 3.3 in 100,000 and 2.15 in 100,000 live births, respectively. Population-based studies have shown the incidence to be almost identical between males and females.[2]

Insight into the genetics of exstrophy has been gleaned from family studies, facilitated by the fact that exstrophy patients are now more likely to produce offspring than in the past. The risk of recurrence of bladder exstrophy in a given family has been estimated to be approximately 1 in 100.[3] A report of seven cases of familial bladder exstrophy and epispadias found inheritance patterns between siblings, third-degree cousins and uncle/nephew pairs, which suggest a complex inheritance phenomenon involving multiple genes and possibly an environmental component.[4]

Whereas nongenetic risk factors appear to play a role in the appearance of these defects, definitive information relating to biologic and environmental contributors is lacking. The incidence of bladder exstrophy or epispadias appears to be higher with decreased maternal age, higher parity,[1] and Caucasian race.[2] Conception through the use of in vitro fertilization has also been implicated in higher incidences of exstrophy.[5] With respect to endogenous teratogens, a Brazilian report found that misoprostol exposure increases the incidence of exstrophy as well as other congenital anomalies.[6] Finally, a geographic variation within the United States showing higher incidences in the South and Midwest and lower incidences in the West[2] indicates again that environmental factors may be significant.

Embryology

Bladder exstrophy (60% of patients within the complex), epispadias (30%), and cloacal exstrophy or minor variants (10%) result from the failure of the cloacal membrane to be reinforced by the ingrowth of mesoderm. Normally, ingrowth of mesenchymal tissue between the ectodermal and endodermal layers of the cloacal membrane forms the lower abdominal musculature and pelvic bones.[7] According to the theory by Marshall and Muecke,[8] an abnormal development of the cloacal membrane prohibits this medial migration, resulting in an unstable embryonic state subject to premature rupture. The timing of this perforation determines whether it will result in cloacal exstrophy, bladder exstrophy, or epispadias.[9]

Examples of classic bladder exstrophy in a male and a female infant are shown in Figures 30-1 and 30-2, respectively.

Morphogenetic models of exstrophy development have been predominantly based on observations from affected fetuses and from what is known about normal embryologic development. Manner and Kluth[10] reported a chick embryo model of cloacal exstrophy, found serendipitously during experiments involving fetal exposure to the teratogen, suramin. They noted that 4 of their 50 experimental animals displayed malformations similar to cloacal exstrophy and subsequently collected embryos displaying cloacal malformations, including abnormal ventral perforation.

Anatomic Considerations

Pelvic Bony Defects

The pelvis in exstrophy patients demonstrates widening of the pubic symphysis and eversion of the innominate bones. Comparing computed tomographic (CT) data between normal children and those with exstrophy, there is a mean external rotation of the posterior aspect of the pelvis of 12 degrees on each side, retroversion of the acetabulum, a mean 18 degrees of external rotation of the anterior pelvis, along with 30% shortening of the pubic rami (Fig. 30-3).[11] Other studies[12] have revealed that the posterior pelvic deformity is caused, at least in part, by the sacroiliac joints' being externally rotated 9.9 degrees more than normal, with an inferior rotation of the pelvis on the order of 14.7 degrees in the superoinferior plane. In cloacal exstrophy, the pelvic deformities are more extreme and more asymmetric and occasionally involve hip dislocation.[11]

Outward rotation and lateral displacement of the innominate bones accounts for the increased distance between the hips, the waddling gait, and outward rotation of the lower limbs in these children, features that cause minimal disability as they grow older.

The inherent potential for growth and development appears to be normal; histologic bone analysis of 28- to 30-week fetuses with classic and cloacal exstrophy, compared with normal fetuses of the same age, showed no difference in microscopic growth patterns or endochondral ossification.[13]

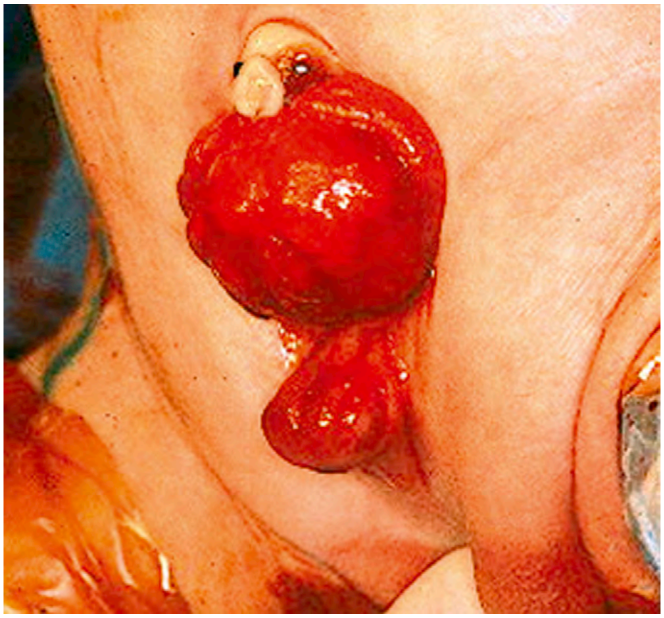


Figure 30-1 Male with classic bladder exstrophy. Notice the excellent size of the bladder template and the reasonably good size of the phallus.

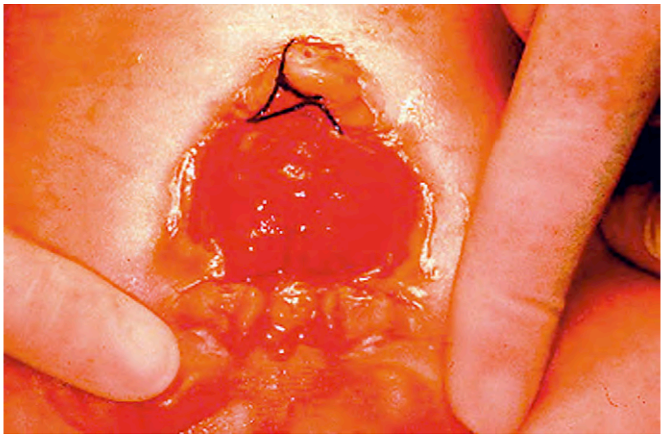


Figure 30-2 Newborn female with classic bladder exstrophy. Notice the size of the bladder template, the vaginal opening, and the bifid nature of the clitoral halves and labia minora.

Pelvic Muscular Defects

The pelvic floor musculature, by supporting the bladder and uterus, plays an important role in fecal and urinary continence, as well as the prevention of organ prolapse. Advanced three-dimensional CT[14] and magnetic resonance imaging (MRI)[15] of patients before reconstruction have demonstrated the exact anatomic deficits and explain why incontinence and prolapse are frequent problems for those with exstrophy. Compared with controls, the levator ani in these patients has almost twice the surface area (9.5 versus 4.5 cm^2) and is therefore subject to twice the load from the pelvic cavity. There is also a flattening of the normal funnel shape. Normally, 48% of the levator ani lies anterior to the rectum and is positioned to support the urethra and bladder. In contrast, the levator ani in exstrophy patients has a significantly shorter anterior segment and longer posterior segment, with only 32% of the muscle located anterior to the rectum (Fig. 30-4). Therefore, the majority of the levator ani is not in an appropriate position to maintain a closed bladder neck and posterior urethra.

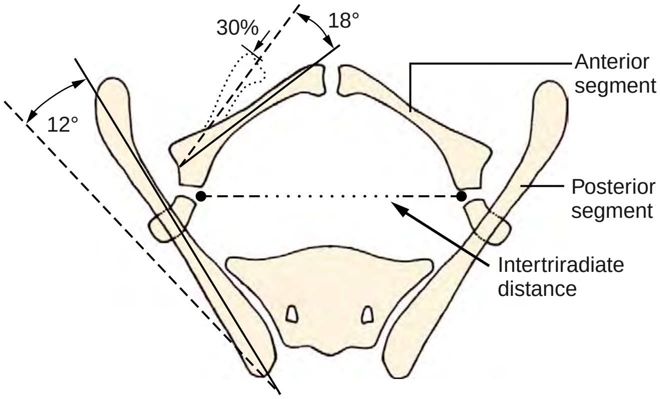


Figure 30-3 Bony deficit in the pelvis of patients with bladder exstrophy. The posterior segment is externally rotated to a mean of 12 degrees on each side, but the length is not different. The anterior segment is externally rotated 18 degrees (6 degrees more than the posterior segment) and is shortened by a mean of 30%. As a result of these changes, the distance between the triradiate cartilages is increased by 31%. (From Gearhart JP. Exstrophy, epispadias, and other bladder anomalies. In: Walsh PC et al., eds. *Campbell's Urology*. Vol 3. 8th ed. Philadelphia: WB Saunders; 2002:2141.)

Divergence of the pelvic floor muscles results in a widening and lengthening of the hiatus through which the urethra, vagina, and rectum pass. The exstrophic pelvic floor has a twofold increase in its transverse width and a 1.3-fold increase in its length. Therefore, in an uncorrected pelvis, organ prolapse is seen as a common complication.

We suspect that repositioning the levator group and decreasing the size of the hiatus contributes to continence[16] and prevention of prolapse. During primary closure, meticulous mobilization and placement of the bladder and posterior urethra deep in the pelvis is essential.

Abdominal Wall Defects

The triangular defect caused by the premature rupture of the abnormal cloacal membrane is occupied by the exstrophied bladder and posterior urethra. The fascial defect is limited inferiorly by the intrasymphyseal band, which represents the divergent urogenital diaphragm. This band connects the bladder neck and posterior urethra to the pubic ramus on anatomic study.

In bladder exstrophy, the distance between the umbilicus and the anus is always foreshortened. Because the umbilicus is situated well below the horizontal line of the iliac crest, there is an unusual expanse of uninterrupted abdominal skin.

The frequent occurrence of an indirect inguinal hernia is attributed to a persistent processus vaginalis, large internal and external inguinal rings, and a lack of obliquity of the inguinal canal. In a review of 181 children with bladder exstrophy, Connelly and coworkers[17] reported inguinal hernias in 81.8% of boys and 10.5% of girls. At the time of closure of the bladder exstrophy, both sides must be explored, and all hernias should be repaired by excision of the hernia sac and repair of the transversalis fascia and muscle defect.

Male Genital Defects

The male genital defect is severe and is the most troublesome aspect of the surgical reconstruction. Formerly, it was thought that the individual corpora cavernosa were of normal caliber

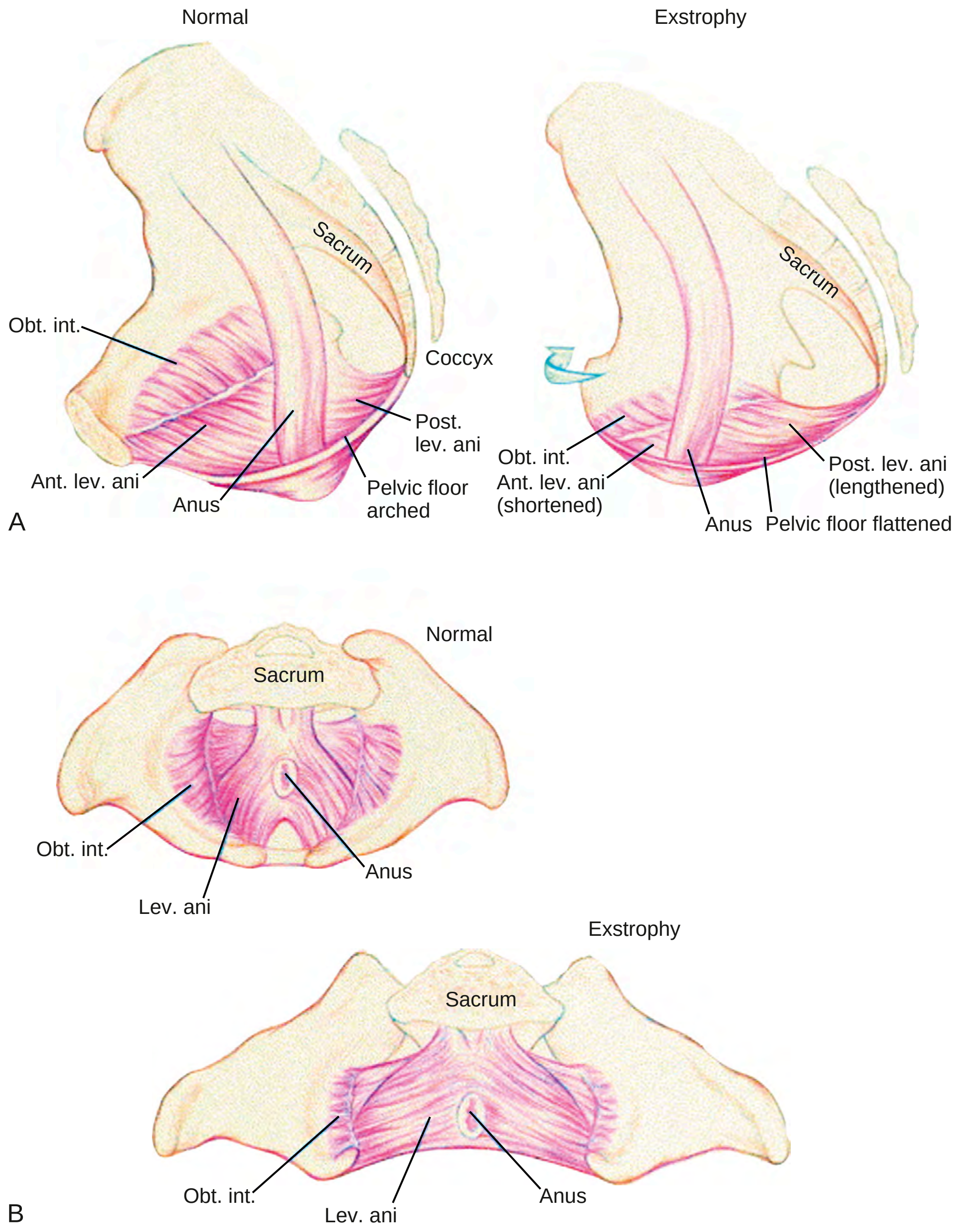

Normal
Exstrophy
Sacrum
Obt. int.
Coccyx
Post. lev. ani
Ant. lev. ani
Anus
Pelvic floor arched
A
Sacrum
Obt. int.
Ant. lev. ani (shortened)
Post. lev. ani (lengthened)
Anus
Pelvic floor flattened
Normal
Sacrum
Obt. int.
Lev. ani
Anus
Exstrophy
Sacrum
Obt. int.
Lev. ani
Anus
B

Figure 30-4 **A,** Displacement of the levator ani *(lev. ani)* to a more posterior position in patients with exstrophy, such that 68% of the muscle lies posterior to the anus, compared with the normal 52%. Consequently, only 32% of the anterior segment of the levator ani lies anterior to the anus, compared with 48% in controls. *Ant.*, anterior; *Obt. int.*, obturator internus; *Post.*, posterior. **B,** There is greater outward rotation of the obturator internus (15.1 degrees) in exstrophy patients versus controls. Also note that the area encompassed by the puborectalis is twice as large as that of controls and more flattened. (From Stec AA, Pannu HK, Tadros YE, et al. Pelvic floor anatomy in classic bladder exstrophy using 3-dimensional computerized tomography: initial insights. *J Urol.* 2001;166:1444.)

but appeared shorter because of the wide separation of the crural attachments, the prominent dorsal chordee, and the shortened urethral groove.

However, 1997 data by Silver and associates[18] described the exact genital defect in bladder exstrophy in greater detail. Using MRI in adult men with exstrophy and comparing them with age- and race-matched controls, it was found that the anterior corporal length was almost 50% shorter (Fig. 30-5). Although the posterior length of the corporal body was the same as that of age-matched controls, the diameter of the posterior corporal segment was approximately 40% larger. It was also found on MRI that, although the diastasis of the symphysis pubis increased the intrasymphyseal and intracorporal distances, the angle between the corpora cavernosa was unchanged because the corporal bodies were separated in a parallel fashion. Therefore, the penis appears short also because of a marked congenital deficiency of anterior corporal tissue.

No functional studies existed concerning the prostate gland before 1997, when Silver and colleagues[19] reported free and total prostate-specific antigen levels for a group of adult men with bladder exstrophy. Although measurable, the

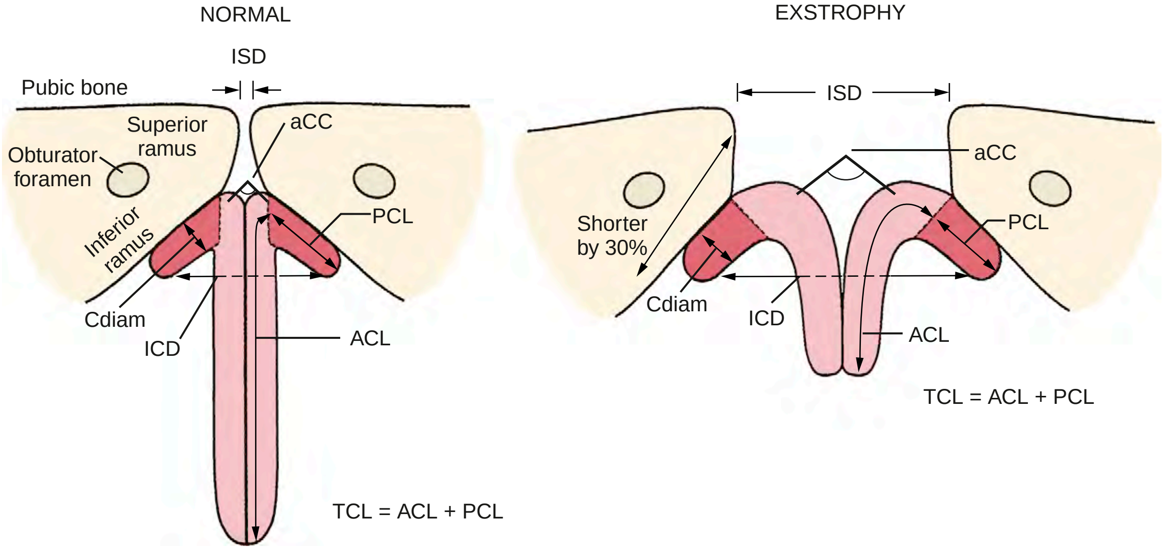


Figure 30-5 Male genital defect in patients with bladder exstrophy. The penile and pelvic measurements in normal men and in patients with exstrophy. aCC, corporal cavernosa subtended angle; ACL, anterior corporal length; Cdiam, corpus cavernosum diameter; ICD, intracorporal distance; ISD, intersymphyseal distance; PCL, posterior corporal length; TCL, total corporal length. (From Silver RI, Yang A, Ben-Chaim J, et al. Penile length in adulthood after exstrophy reconstruction. *J Urol*. 1997;157:999.)

levels were below the upper limit for established age-specific reference ranges for healthy men. The vas deferens and ejaculatory ducts are normal in these patients, provided they are not injured iatrogenically. In a 1993 study by Gearhart and coworkers,[20] 13 men born with bladder exstrophy underwent MRI of the pelvis to evaluate the size and configuration of the prostate and pelvic organs. The volume, weight, and maximal cross-sectional area of the prostate appeared normal compared with those of published controls. In none of the patients did the prostate extend circumferentially around the urethra, and the urethra was anterior to the prostate in all patients. The mean seminal vesicle length and width were normal compared with those of published controls. Evaluation of the puborectalis muscles found them to be widely separated and to provide only lateral support of the prostate in patients who were continent and had undergone prior posterior iliac osteotomy.

Autonomic innervation of the corpus cavernosum is provided by the cavernous nerves. These autonomic nerves are displaced laterally in exstrophy patients.[21] Potency is preserved in almost all patients, but retrograde ejaculation may occur.

The testes frequently appear undescended in their course from the widened, separated pubic tubercles to the flat, wide scrotum, but they have an adequate length of spermatic cord to reach the scrotum without the need for orchiopexy.

Female Genital Defects

Reconstruction of the female genitalia presents a less complex problem than in the male (see Fig. 30-2). The vagina is shorter than normal, rarely greater than 6 cm in depth, but of normal caliber. The vaginal orifice is frequently stenotic and displaced anteriorly; the clitoris is bifid; and the labia, mons pubis, and clitoris are divergent. The uterus enters the vagina superiorly so that the cervix is in the anterior vaginal wall. The fallopian tubes and ovaries are normal. The clitoral halves should be joined to make a fourchette at the time of primary closure. Vaginal dilation or episiotomy may be required to allow satisfactory intercourse in the mature female. The defective pelvic floor predisposes to uterine prolapse, in which case uterine suspension will be necessary. This usually occurs after childbirth but may be seen in the nulliparous patient. Uterine prolapse is less common when osteotomy and primary closure of the anterior defect are performed early in life.

Urinary Defects

At birth, the bladder mucosa may appear normal; however, hamartomatous polyps may be present on the bladder surface, representing squamous metaplasia and, commonly, cystitis glandularis.[22] Such findings warrant future surveillance with bladder cytology and cystoscopy. If the bladder mucosa is not frequently irrigated with saline solution and protected from surface trauma by the interposition of some form of protective membrane before closure, cystic or metaplastic changes in the mucosal surface may occur.[22]

Many basic science studies have been published that further delineate the exact nature of the exstrophied bladder in the newborn. Work by Shapiro and associates[23] in 1985 showed that the density and binding affinity of muscarinic cholinergic receptors was similar in exstrophied and normal bladders. Mathews and colleagues[24] used electron microscopy to evaluate the histology of bladder tissue in newborns before closure, in patients undergoing reclosure after failure, in patients undergoing bladder neck reconstruction, and also at the time of augmentation cystoplasty. They found that future continence correlated with a normal or near-normal ultrastructure with regard to smooth muscle arrangement, preservation of mitochondria, presence of caveolae, and nerve profiles.

Several studies have investigated both the neural innervation of the newborn exstrophied bladder and its muscle and collagen content. Mathews and colleagues[25] looked at myelinated nerve density in the newborn with bladder exstrophy compared with newborn controls and found a statistically significant decrease in the former. The reduction in nerve fibers appeared to be due to a lack of small fibers with preservation of larger nerve fibers, which likely represents a maturational delay in overall development. Lee and coworkers,[26] looking at bladder biopsies obtained from 12 newborns with bladder exstrophy compared with age-matched controls, found an increase in the collagen-to-smooth muscle ratio in the former. Compared with healthy control bladders, there was no statistical difference in the amount of type I collagen of exstrophied bladders at the time of initial closure. However, there was a threefold increase in type III collagen. In patients who gained adequate bladder capacities and were awaiting bladder neck reconstruction, Peppas[27] and Lais[28] and their coworkers independently found that the ratio of collagen to smooth muscle decreased markedly after a successful closure and infection-free follow-up. Orsola and associates[29] produced primary cultures of smooth muscle cells from normal and exstrophied bladders. They found that the growth pattern of exstrophied smooth muscles was similar to that of normal tissue and that the increased growth response induced by mechanical stretch cycles was retained. Therefore, although these studies revealed that exstrophy in a newborn may represent a maturational delay in bladder development, the tissue does have the potential for normal functional anatomy after successful closure.

The upper urinary tract is usually normal, and the peritoneal pouch of Douglas, between the bladder and the rectum, is enlarged and unusually deep, forcing the ureter down laterally in its course across the true pelvis. The distal segment of the ureter approaches the bladder from a point inferior and lateral to the orifice, and it enters with no obliquity. Therefore, reflux in the closed exstrophy bladder occurs in 100% of cases, and correctional surgery is required at the time of bladder neck reconstruction.

Prenatal Diagnosis and Management

Ultrasound evaluation of the fetus by means of high-resolution real-time units allows a survey of fetal anatomy even during routine obstetric ultrasonography. In a review of 25 prenatal ultrasound examinations with the resulting birth of newborns with classic bladder exstrophy, several observations were made: (1) absence of a fluid-filled bladder, (2) a low-set umbilicus, (3) widening of the pubic rami, (4) diminutive genitalia, and (5) a lower abdominal mass that increased in size as the pregnancy progressed and as the intra-abdominal viscera increased in size.[30] Further case reports have exploited the power of color Doppler sonography to identify the perivesical umbilical arteries, which run alongside the bladder until they enter the umbilical cord.[31,32] These landmarks help to differentiate other possible causes of abdominal masses found on ultrasound images. Quality of ultrasound imaging is enhanced by the use of surface rendering to produce three-dimensional images.[33] In equivocal cases, MRI has been used to overcome obstacles such as maternal body habitus, fetal position, and oligohydramnios; however, it should be considered a second-line investigation.[34] Prenatal diagnosis of bladder exstrophy allows optimal prenatal management, including delivery in a pediatric center prepared to handle this complex malformation and appropriate prenatal counseling of the parents about the nature of the congenital malformation.

Modern Surgical Reconstruction

Since the mid-1990s, the modern staged repair of exstrophy (MSRE)[35,36] has included bladder, posterior urethra, and abdominal wall closure in the newborn period with bilateral innominate and vertical iliac osteotomy, if indicated; epispadias repair at 6 to 12 months of age; and bladder neck reconstruction along with an antireflux procedure at the age of 4 to 5 years, when the child has achieved adequate bladder capacity and is motivated to participate in a postoperative voiding program.[37]

Other methods of treatment for the newborn with bladder exstrophy have been developed. Grady and Mitchell[38] proposed combining bladder exstrophy closure with epispadias repair in the newborn period. Baka-Jakubiak[39] in Poland recommended newborn exstrophy closure alone, with combined bladder neck reconstruction and epispadias repair when the child reaches a satisfactory age for participation in a voiding program. Schrott and colleagues[40] have recommended bladder closure, ureteral reimplantation, epispadias repair, and bladder neck reconstruction in the newborn period. Finally, Stein and coworkers[41] recommended ureterosigmoidostomy in the newborn period with abdominal wall and bladder closure.

Patient Selection

Successful treatment of exstrophy by functional closure demands that the potential for success in each child be carefully considered at birth. The size and functional capacity of the detrusor muscle are important considerations in the eventual success of functional closure. The apparent bladder size must not be confused with potential bladder capacity. The bladder may appear small yet demonstrate acceptable capacity, either by bulging when the baby cries or by indenting easily when touched by a sterile gloved finger in the operating room, with the child under anesthesia. Sometimes a good bit of previously unappreciated bladder is discovered behind the fascia during examination under surgery. Once removed from surface irritation and repeated trauma, the small bladder can enlarge.

Delivery Room and Nursery

At birth, although the bladder mucosa is usually smooth, pink, and intact, it is also sensitive and easily denuded. After delivery, the umbilical cord should be tied with 2-0 silk close to the abdominal wall, to prevent the umbilical clamp from traumatizing the mucosa and causing excoriation. The bladder should be covered with a nonadherent film of plastic wrap (e.g., Saran Wrap) to prevent the mucosa from sticking to the diaper or clothing. Each time the diaper is changed, the plastic wrap should be changed and the bladder surface irrigated with sterile saline solution.

Given the severity of these birth defects and the great emotional stress placed on the parents, extensive counseling is warranted, ideally using an exstrophy support team approach. This team should consist of a surgeon with a special interest and experience in dealing with exstrophy, a pediatric orthopedic surgeon, a pediatric anesthesiologist, social workers, nurses with experience in exstrophy, and a child psychiatrist with expertise in genital anomalies. Further educational materials are available on Web sites maintained by the Association of Bladder Exstrophy Children and several major exstrophy centers.

Early Management

Cardiopulmonary and general physical assessment can be carried out immediately after delivery. Ultrasound studies can provide evidence of normal renal appearance before the patient undergoes closure of the exstrophy defect.

In less than ideal circumstances, a thorough neonatal assessment may have to be deferred until transfer of the baby to a major children's medical center. During transportation, the bladder should be protected by a plastic membrane.

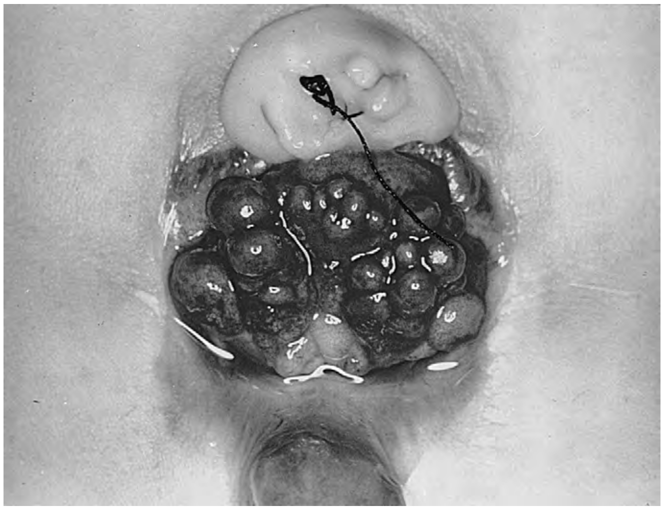


Figure 30-6 Small, inelastic bladder template covered with polyps, unsuitable for closure.

Exstrophic Bladder Unsuitable for Closure

Decisions concerning the adequacy of a bladder for closure or delayed repair carry much gravity in terms of long-term consequences and should be made by surgeons with a great deal of experience in the bladder exstrophy condition. A small fibrotic bladder patch that is stretched between the edges of a small triangular fascial defect without elasticity or contractility cannot be selected for a usual closure procedure (Fig. 30-6).

Dodson and associates[42] reported on 19 patients at one institution who were initially judged to have bladders too small for immediate closure. After a delay of 6 to 23 months, bladder size had increased to the point that closure and concomitant epispadias repair was appropriate. Long-term follow-up revealed that 50% of these patients were dry after bladder neck reconstruction, and the remaining 50% required other adjunctive procedures.

Delaying closure while the bladder grows carries some risk in terms of bladder degradation due to inflammation or infection, and these children do have an increased need for further augmentation. However, this is preferable to subjecting an inappropriately small bladder to closure, which is likely to result in dehiscence and an unsalvageable bladder. After 6 to 12 months or more of delay, if the bladder is still not of appropriate size for closure, a colon conduit is the procedure of choice.

Surgical Procedure

Since the early 1980s, modifications in the management of functional bladder closure have contributed to a dramatic increase in the success of the procedure. The most significant changes have been (1) early bladder, posterior urethra, and abdominal wall closure, usually with pelvic osteotomy; (2) early epispadias repair; (3) reconstruction of a competent bladder neck and reimplantation of the ureters; and, most importantly, (4) defining strict criteria for the selection of patients suitable for this approach.

OSTEOTOMY

Pelvic osteotomies performed at the time of closure confer advantages, including (1) easy reapproximation of the symphysis with diminished tension on the abdominal wall closure and elimination of the need for fascial flaps, (2) placement of the urethra deep within the pelvic ring, and (3) ability to bring the large pelvic floor muscles toward the midline, where they can support the bladder neck and aid in eventual urinary control. In a review of a large number of patients with failed exstrophy procedures referred to our institution, most of those referred with partial or complete dehiscence of the bladder, as well as those with major bladder prolapse, had not undergone prior osteotomy.[43]

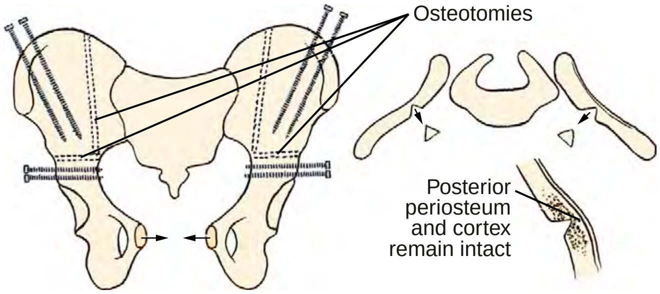


Figure 30-7 Combined transverse anterior innominate and anterior vertical iliac osteotomy with pin placement and preservation of the posterior periosteum and cortex. (From Gearhart JP, Forschner DC, Jeffs RD, et al. A combined vertical and horizontal pelvic osteotomy approach for primary and secondary repair of bladder exstrophy. *J Urol.* 1996;155:689.)

Our recommendation is to perform bilateral transverse innominate and vertical iliac osteotomies when the bladder closure is performed after 72 hours of age. In addition, if the pelvis is not malleable or if the pubic bones are greater than 4 cm apart at the time of initial examination under anesthesia, osteotomy should be performed, even if closure occurs before 72 hours of age.

If examination under anesthesia reveals the pubic bones to be malleable and able to be brought together easily, the patient can undergo closure without osteotomy. However, if there is any doubt regarding this decision, osteotomy should be performed. Improved approximation lessens the tension on the midline abdominal closure and decreases the rate of bladder dehiscence and prolapse.[37] In addition, pubic closure allows approximation of the levator ani and puborectalis sling, inclusion of the bladder neck and posterior urethra deep within the pelvic ring, and an improved continence rate. In addition to ease of approximation, anterior innominate osteotomy combined with vertical iliac osteotomy was developed for three reasons: (1) the procedure can be performed with the child in the supine position, as in the urologic repair; (2) it allows placement of an external fixator device and intrafragmentary pins under direct vision; and (3) the cosmetic appearance is superior to that of other approaches.

With the patient in a supine position, transverse and posterior osteotomies are performed (Fig. 30-7).[44] Radiographs are obtained to confirm pin placement, soft tissues are closed, and the urologic repair is performed.

Postoperative pelvic immobilization has a significant impact on the success of the operation.[45] After repair with osteotomy, we use 4 to 6 weeks of modified Buck's traction (Fig. 30-8) and keep the external fixator on for approximately 6 weeks until a radiograph shows adequate calculus at the site of osteotomy. Newborns undergoing repair without osteotomy may be immobilized with modified Bryant's traction (Fig. 30-9) for 4 weeks. Given the high rate of failure and complications, spica cast and "mummy wrapping" techniques are not recommended.

After good callus formation is seen on radiographs, the fixating device and pins are removed. Although both classic and cloacal exstrophy patients gained approximation from

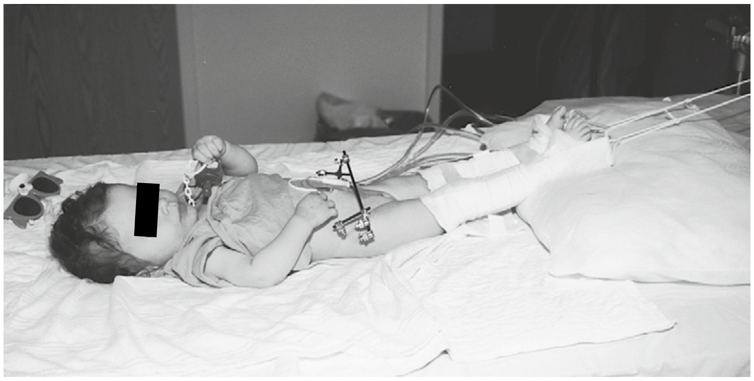


Figure 30-8 Fixator position and light Buck's traction on the legs in a 20-month-old child with reclosure of bladder exstrophy after two previous closures. Note tubes exiting the neoumbilicus and no tubes exiting the urethra.

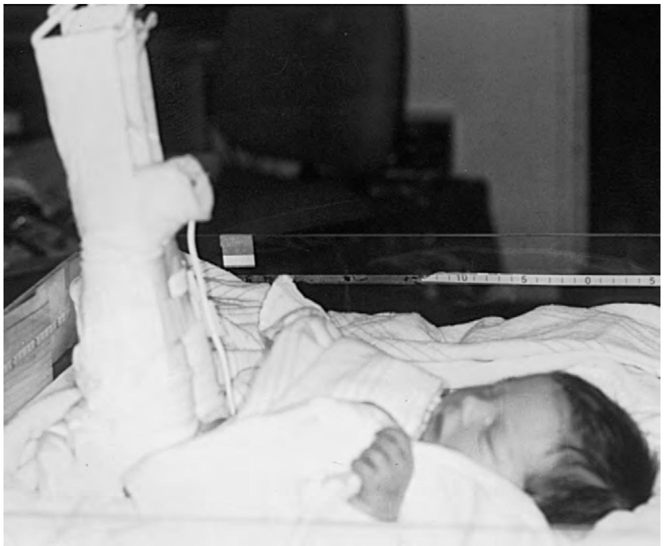


Figure 30-9 Modified Bryant's traction in a newborn who underwent closure without pelvic osteotomy. This traction is maintained for 4 full weeks.

osteotomy, the former demonstrated a greater correction toward normal, presumably due to better bone quality.[46] Greater preoperative diastasis and less optimal bone density in the newborn contribute to greater difficulty obtaining and maintaining closure of the pelvic bony deformity over time. Partial recurrence of diastasis in classic exstrophy most likely occurs by two mechanisms. First, the pelvis may partially derotate due to early loosening of pins, before the time of osteotomy healing. In the older child, increased bone density allows more rigid external fixation, providing better maintenance of the corrected position. Second, there is long-term undergrowth of the ischiopubic segment, which has been shown to be 33% less than normal in the adult with exstrophy as the pelvis grows. Even with some loss of approximation, there is still significant correction, and a strong intrasymphyseal band remains.

The role of osteotomy is to remove tension on the bladder, posterior urethral wall, and abdominal wall repair during healing. We use osteotomy rarely in newborns and young infants, because ligament laxity allows the pelvis to be closed without tension. However, it becomes essential in the older child with a failed exstrophy repair, in the patient with cloacal exstrophy, and in the newborn with wide diastasis and excellent bladder template. In patients undergoing combined exstrophy closure and epispadias repair, osteotomy allows the pubis to be joined, which helps when positioning the corpora over the closed proximal urethra.[47]

Bladder, Posterior Urethral, and Abdominal Wall Closure

The sequential steps in primary closure are illustrated in Figure 30-10. Before and during the procedure, the patient is given wide-spectrum antibiotics in an attempt to convert a contaminated field into a clean surgical wound. Routine use of latex-free gloves, tubes, and catheters is recommended.[48]

Management after Primary Closure

The procedure just described converts a patient with exstrophy into one with proximal shaft epispadias and incontinence. Before removal of the suprapubic tube 4 weeks postoperatively, the bladder outlet is calibrated by urethral catheter or sound to ensure free drainage. An ultrasound examination is obtained to ascertain the status of the renal pelves and ureter, and appropriate urinary antibiotics are administered to treat any bladder contamination that might be present after removal of the suprapubic tube. Residual urine is estimated by clamping the suprapubic tube, and specimens for culture are obtained before the patient leaves the hospital and at subsequent intervals to detect infection. If initial ultrasonography shows good drainage, upper tract imaging by ultrasonography is repeated 3 months after discharge and at intervals of 6 months to 1 year during the next 2 to 3 years to detect any upper tract changes caused by reflux, infection, or silent obstruction.

Prophylactic antibiotic therapy should be continuous, because all patients with bladder exstrophy, once closed, have vesicoureteral reflux. If a useful continence interval has resulted from initial closure, a further operation for incontinence may not be required; however, this situation is quite unusual. In our experience, this has occurred in 3 patients, all of whom were female.

At yearly intervals, gravity cystograms with the patient under anesthesia detect bilateral reflux in almost 100% of patients and provide an estimate of bladder capacity. In some patients with very small bladders, 4 to 5 years may be necessary to achieve adequate capacity. However, if the bladder has not achieved a capacity of at least 30 mL by 1 to 2 years, concern must be voiced to parents about the overall ability of the bladder to undergo a continence procedure.

Should bladder outlet resistance be such that urine is retained within the bladder and high-grade reflux and ureteral dilation develop with infected urine, it may be necessary to dilate the urethra or to begin a program of clean intermittent catheterization. Sometimes, posterior urethral obstruction is severe enough to require a transurethral incision of the stricture to maintain adequate drainage; if this is not effective, surgical revision of the bladder outlet by advancing skin flaps into the orifice or even patching the stricture may be

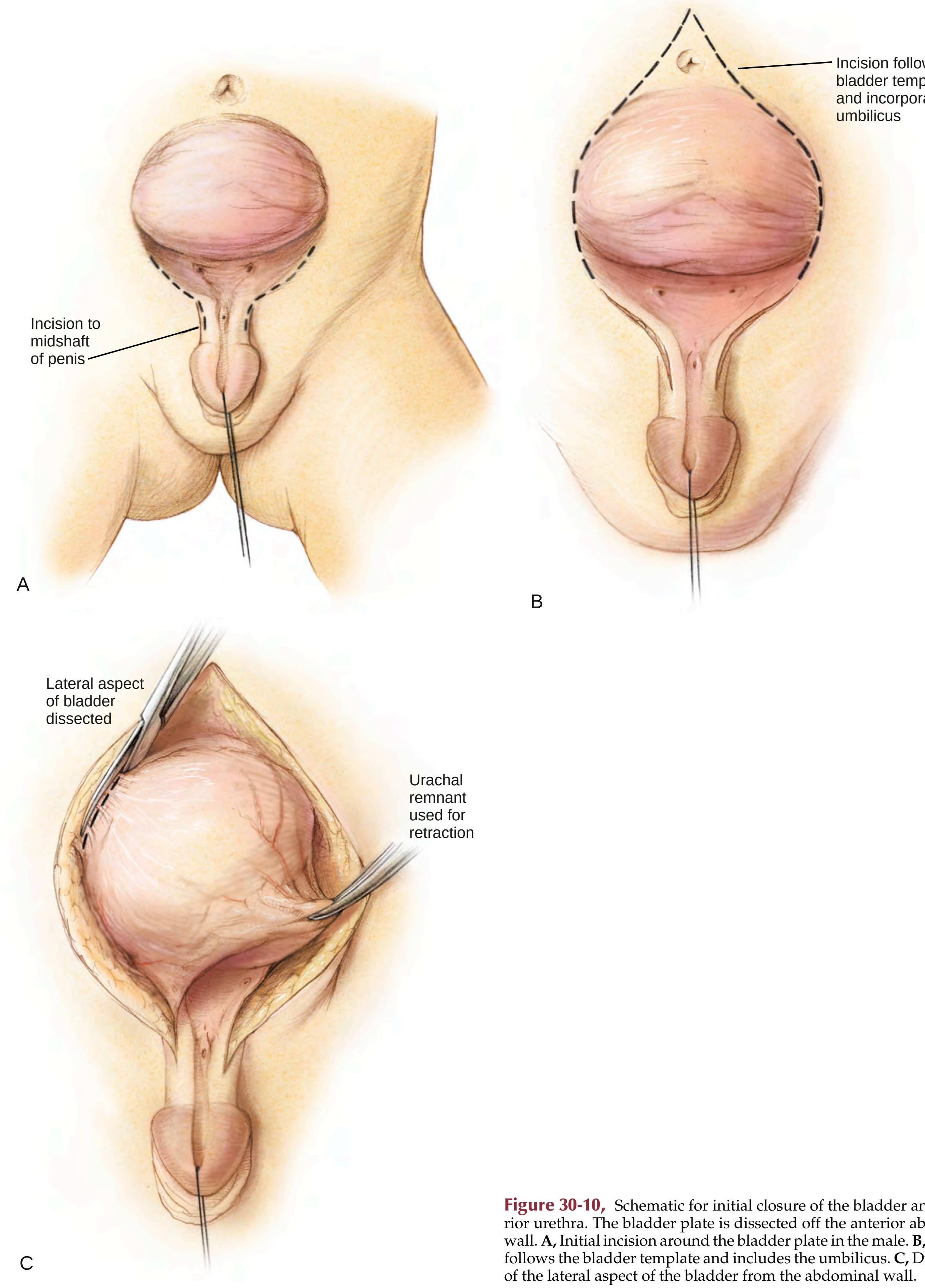

Incision to midshaft of penis
A
Incision follows bladder template and incorporates umbilicus
B
Lateral aspect of bladder dissected
Urachal remnant used for retraction
C

Figure 30-10, Schematic for initial closure of the bladder and posterior urethra. The bladder plate is dissected off the anterior abdominal wall. **A,** Initial incision around the bladder plate in the male. **B,** Incision follows the bladder template and includes the umbilicus. **C,** Dissection of the lateral aspect of the bladder from the abdominal wall.

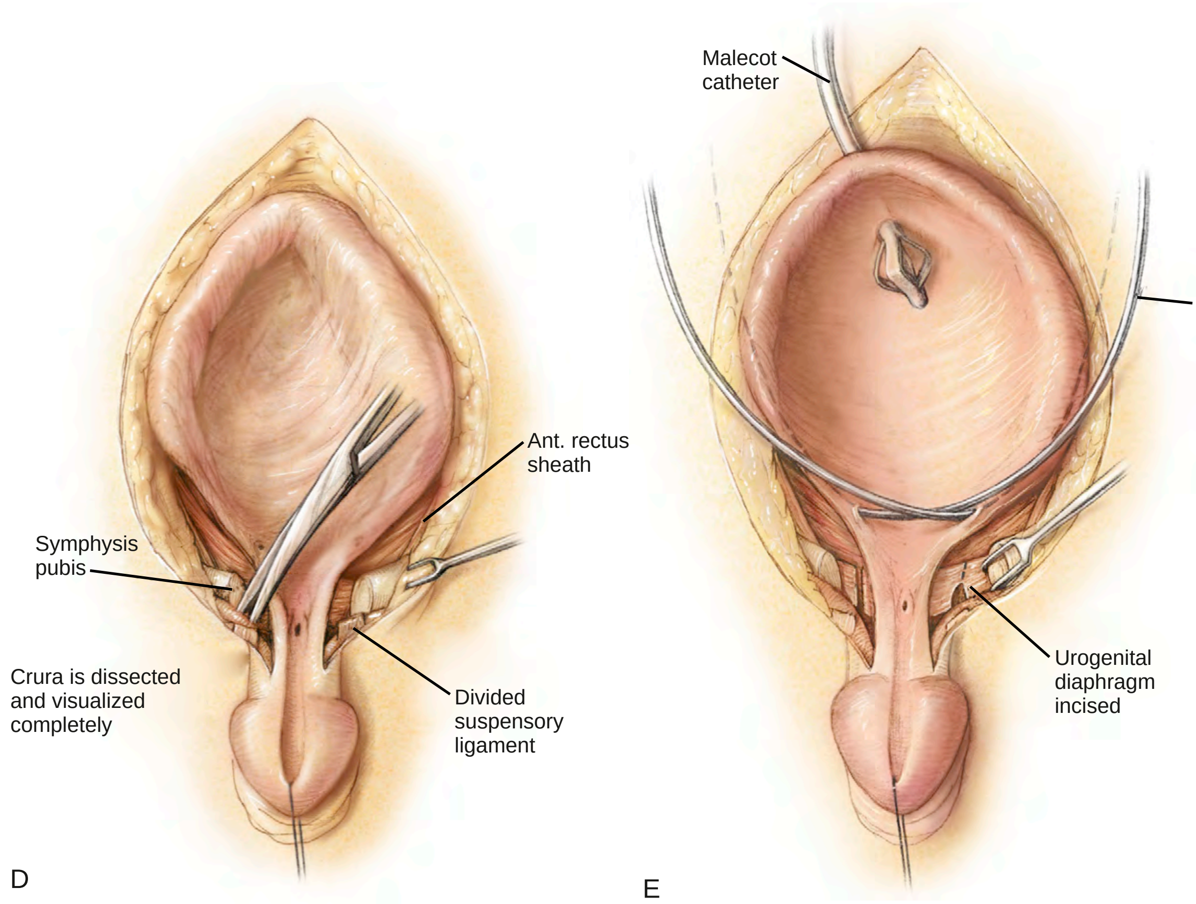

Malecot catheter
Ureteral stents
Ant. rectus sheath
Symphysis pubis
Crura is dissected and visualized completely
Divided suspensory ligament
Urogenital diaphragm incised
D
E

Figure 30-10, cont'd **D,** Dissection of the crura from the symphysis pubis. **E,** Division of the urogenital diaphragm fibers. Note stents and suprapubic tube in place in the bladder.

necessary. In patients who present with recurrent infections or worsening hydronephrosis, early ureteral reimplantation should be performed before bladder neck reconstruction.[49] An important caveat is that, if recurrent urinary tract infections occur yet the bladder is not significantly distended on ultrasonography, cystoscopy should be performed and the posterior urethra should be carefully examined for the infrapubic stitch, as this may be a cause for recurrent infections and should be removed.[50]

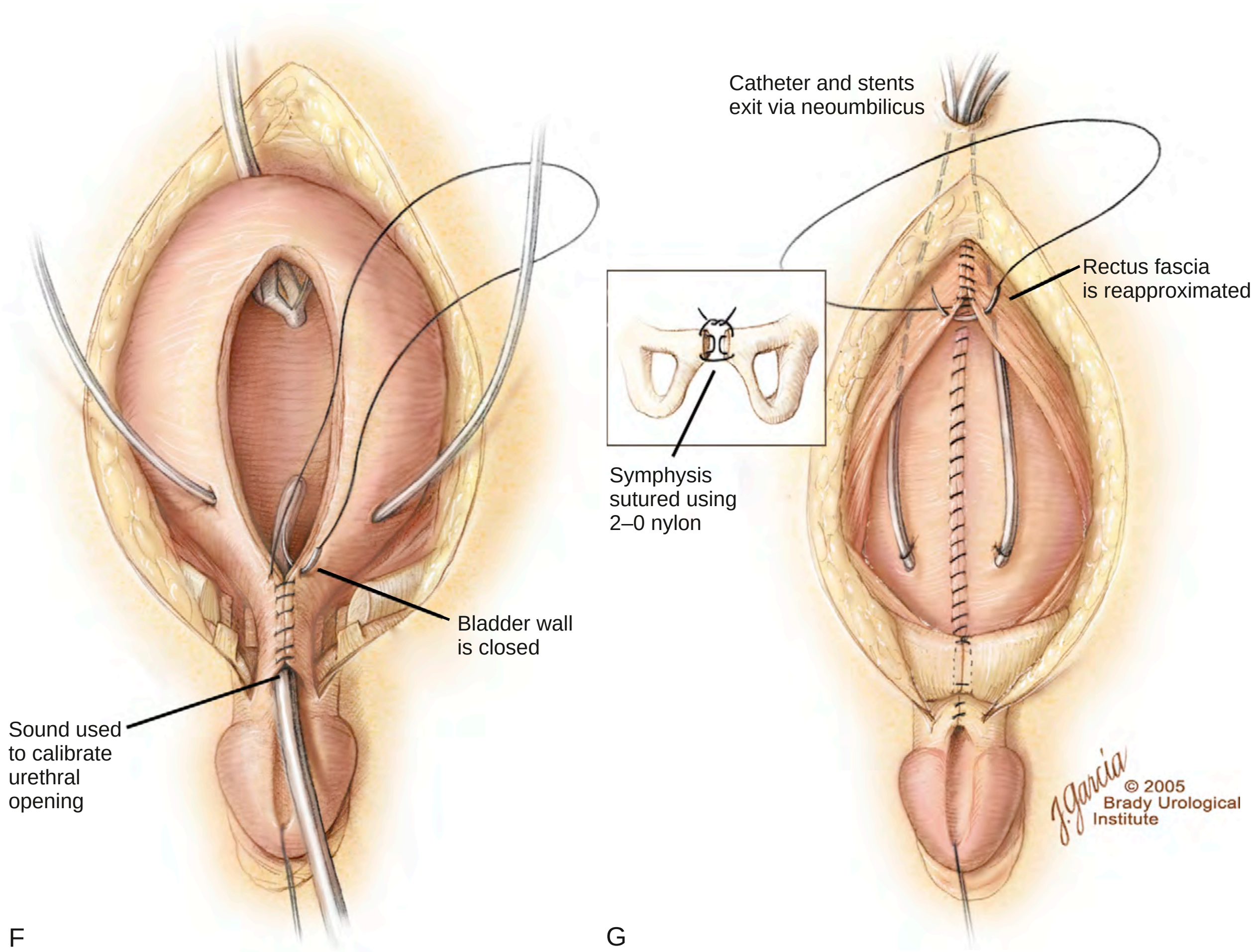
Epispadias Repair

Based on evidence that bladder capacity increases after epispadias repair, the modern staged repair of exstrophy now prescribes that this be done before bladder neck reconstruction.[51] In a group of patients with a small bladder capacity after initial closure, there was a mean increase in capacity to 55 mL only 22 months after epispadias repair. We now perform the repair at 6 months of age in all patients. The objective is to have all patients achieve an appropriate bladder capacity by the time they are physically and mentally ready to undergo bladder neck reconstruction. Because a majority of boys with exstrophy have a somewhat small penis with a paucity of penile skin, all patients undergo testosterone stimulation therapy (intramuscular testosterone enanthate, 2mg/kg at 5 weeks and 2 weeks preoperatively) before urethroplasty and penile reconstruction.[52]

Many surgical techniques have been described for reconstruction of the penis and urethra in patients with classic bladder exstrophy. The most current methods are the Cantwell-Ransley repair,[53] the modified Cantwell-Ransley repair,[54,55] and the penile disassembly technique first described by Mitchell and Bagley in 1996.[56] Our preference for urethroplasty and penile reconstruction is the modified Cantwell-Ransley repair (Fig. 30-11).[56] Regardless of the surgical technique chosen, four key concerns must be addressed to ensure a functional and cosmetically pleasing penis: (1) correction of the dorsal chordee, (2) urethral reconstruction, (3) penile skin closure, and (4) glandular reconstruction.

It is often necessary to perform penile elongation with release of chordee at the time of urethroplasty in exstrophy patients. Certainly, all remnants of the suspensory ligaments and old scar tissue from initial bladder closure must be excised. Also, further dissection of the corpora cavernosa from the inferior pubic ramus can be achieved. It is often surprising how little was accomplished in freeing the corporal bodies from the pubis at the time of initial exstrophy closure.[57]

With modern techniques of epispadias repair, replacement of the urethra is not typically performed. However, in the penile disassembly technique described by Mitchell, the urethral plate is dissected completely free from the glans. In a number of patients, the urethral plate is not long enough to reach the tip of the penis; 70% of the time, this results in a hypospadias that will require further reconstruction.[56] Because of the marked disparity in penile length between exstrophy patients and normal males, we believe that complete detachment of the urethral plate from the glans is an unnecessary step: no additional length will be obtained and the added step of hypospadias repair will be required.


Catheter and stents exit via neoumbilicus
Rectus fascia is reapproximated
Symphysis sutured using 2–0 nylon
Bladder wall is closed
Sound used to calibrate urethral opening
J. Garcia
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F
G

Figure 30-10, cont'd **F,** Initial layer of the bladder closure. The urethral meatus is calibrated to 14F (4.62 mm) in diameter. Stents are brought out of the bladder. **G,** Pubic approximation is performed with no. 2 nylon mattress suture *(inset)*. Abdominal wall closure is completed. The suprapubic tube and stents are brought out through the umbilicus. (Adapted from Gearhart JP, Mathews R. Exstrophy-epispadias complex. In: Wein AJ et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, chapter 119.)

Chordee and Urethral Reconstruction

Besides lengthening of the urethral groove, dorsal chordee must be addressed. To release dorsal chordee, one may lengthen the dorsomedial aspect of the corpora by incision and anastomosis of the corpora themselves.[53] However, by rotating the corpora over the urethra, the majority of chordee is corrected. Other techniques,[58,59] especially grafting of the corona, are reserved for patients seen in adolescent and adult years with failed epispadias surgery and the need for increased penile length and correction of residual chordee.

Urethral reconstruction is an important aspect of external genital reconstruction in exstrophy that can be accomplished by many methods. Modern techniques of epispadias repair associated with bladder exstrophy involve tubularization of the urethral plate and relocation of the urethral plate under the corporal bodies after closure. This lessens the incidence of urethrocutaneous fistula and also gives the penis a more downward deflection and a more easily catheterizable urethral channel.

Penile Skin Closure

Skin closure remains a problem in genital reconstruction because of the paucity of skin associated with this condition. A Z-plasty incision and closure at the base of the penis prevent skin contraction and upward tethering of the penis. The ventral foreskin can be split in the midline (reverse-Byars concept) and brought to the dorsum as lateral preputial flaps for coverage of the penile shaft. Khoury and colleagues[60] overcame this obstacle by creating a ventral preputial transverse island flap, rotated dorsally to cover the dorsal penile shaft, and an advancement flap from penoscrotal skin to cover the ventral surface.

Female Genitalia

Reconstruction of the mons and external genitalia is done at the time of initial exstrophy closure. Although this adds a bit of time to the operation, once the pubic bones are brought into apposition with osteotomy it is quite easy to reconstruct the genitalia.[43] A recent report from Toronto described a simple monsplasty technique that demonstrated good cosmetic results with no complications.[61]

Postoperative Problems

Postoperative pain and bladder spasms after extensive external genitalia reconstructive surgery require a combined effort by the pediatric anesthesia pain service and the surgical service. Control of bladder spasms is paramount, because they are associated with more urinary extravasation and fistula

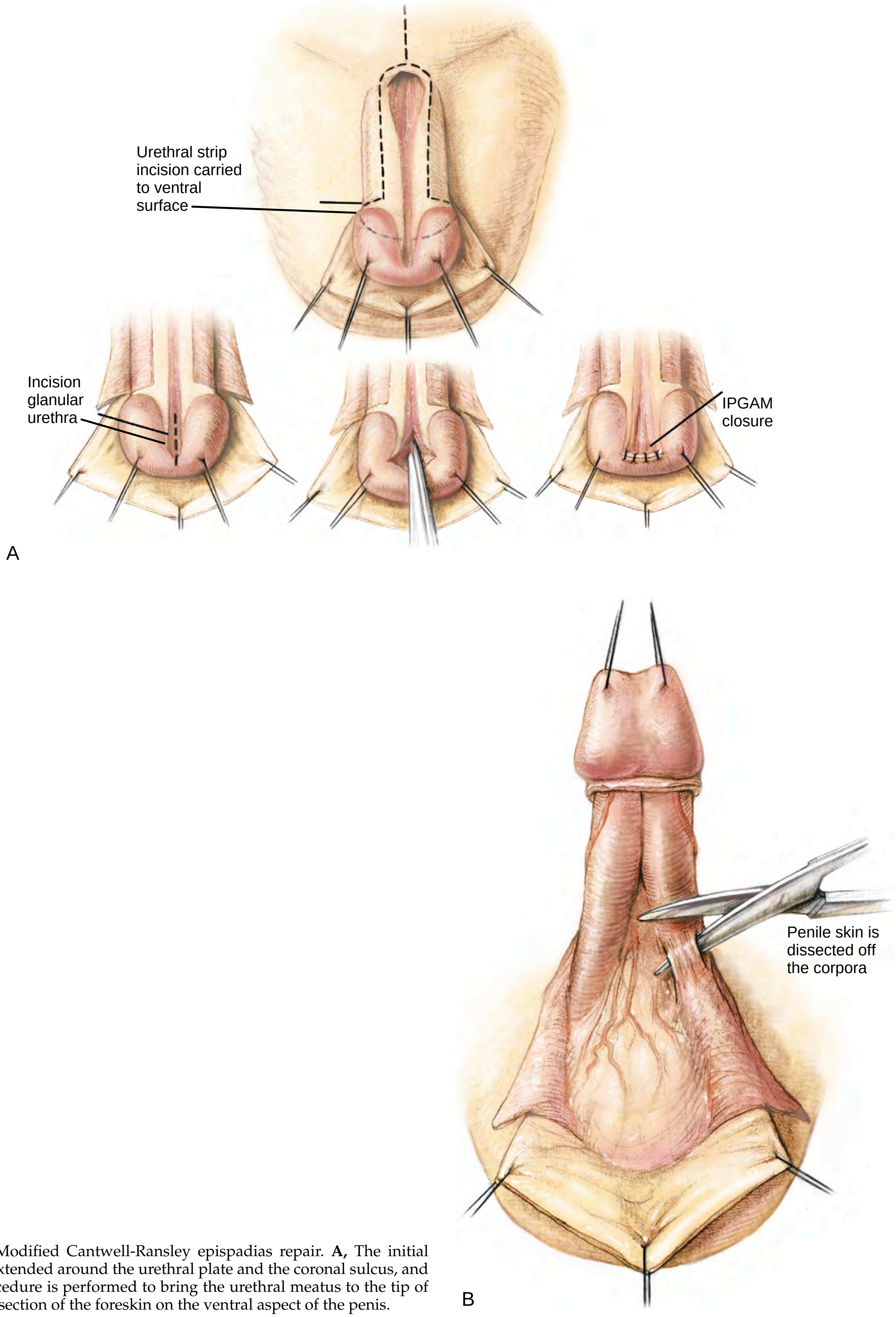

Urethral strip incision carried to ventral surface
Incision glanular urethra
IPGAM closure
A
Penile skin is dissected off the corpora
B

Figure 30-11 Modified Cantwell-Ransley epispadias repair. **A,** The initial incision line is extended around the urethral plate and the coronal sulcus, and the IPGAM procedure is performed to bring the urethral meatus to the tip of the glans. **B,** Dissection of the foreskin on the ventral aspect of the penis.

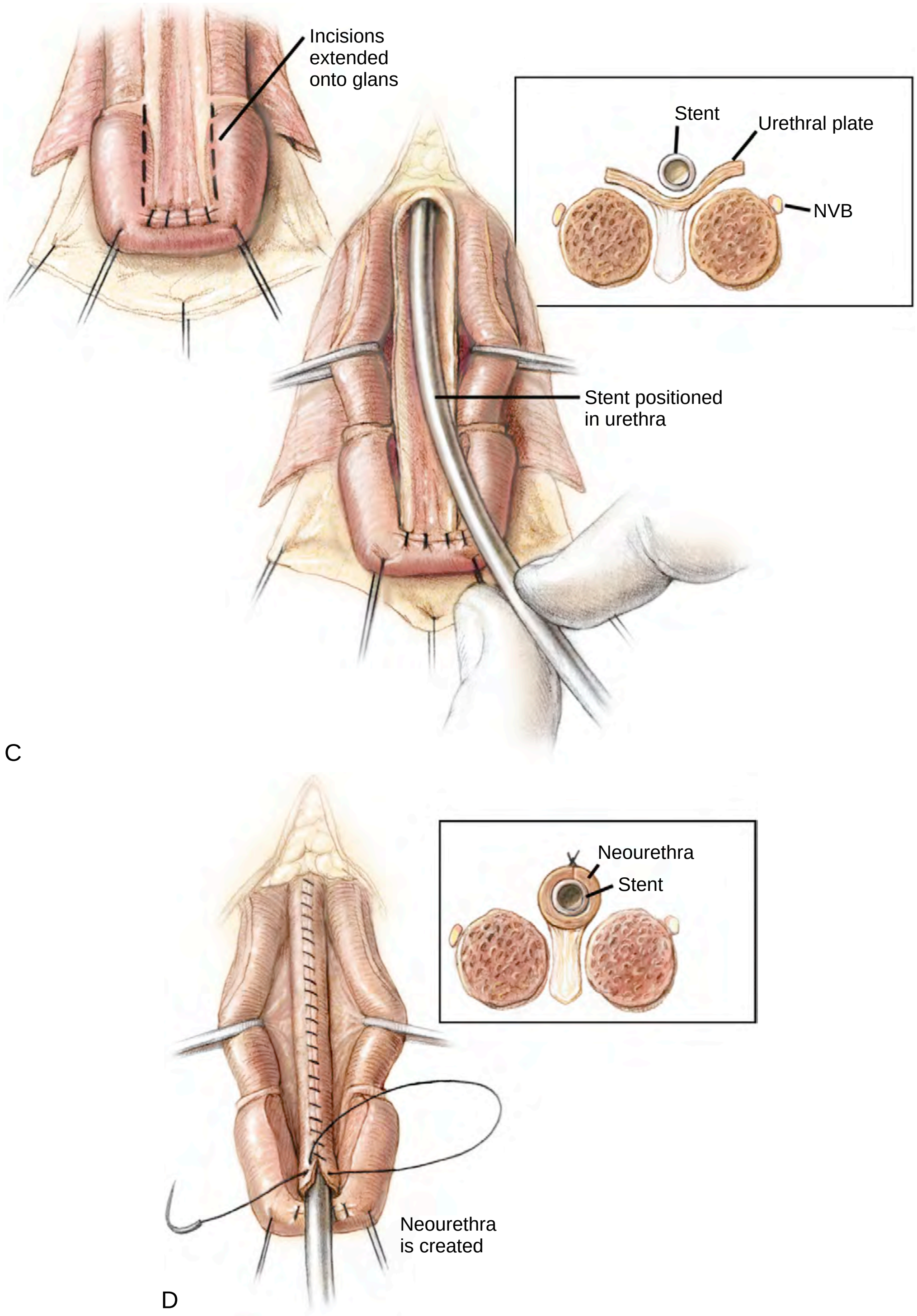

Incisions
extended
onto glans
Stent
Urethral plate
NVB
Stent positioned
in urethra
C
Neourethra
Stent
Neourethra
is created
D

Figure 30-11, cont'd **C,** The corpora are dissected off the urethral plate, and parallel incisions are made into the glans to create glans wings. Note the lateral position of the neurovascular bundles (NVB, *inset*). **D,** The urethra is tubularized with the use of a continuous running suture.

formation. All of our patients have a caudal epidural catheter placed at the time of surgery to help with postoperative pain control and bladder spasms. In addition, oxybutynin therapy is started immediately after surgery. At the time of discharge, the child is provided with narcotics, antispasmodics, and appropriate broad-spectrum antibiotics.

Continence and Antireflux Procedure

Bladder capacity is measured with the child under anesthesia, by means of a gravity cystogram, beginning at the 1-year anniversary of the initial closure. Data from Gearhart and associates[62] demonstrated a median bladder capacity of 100 mL, rather than the previous threshold of 85 mL, in

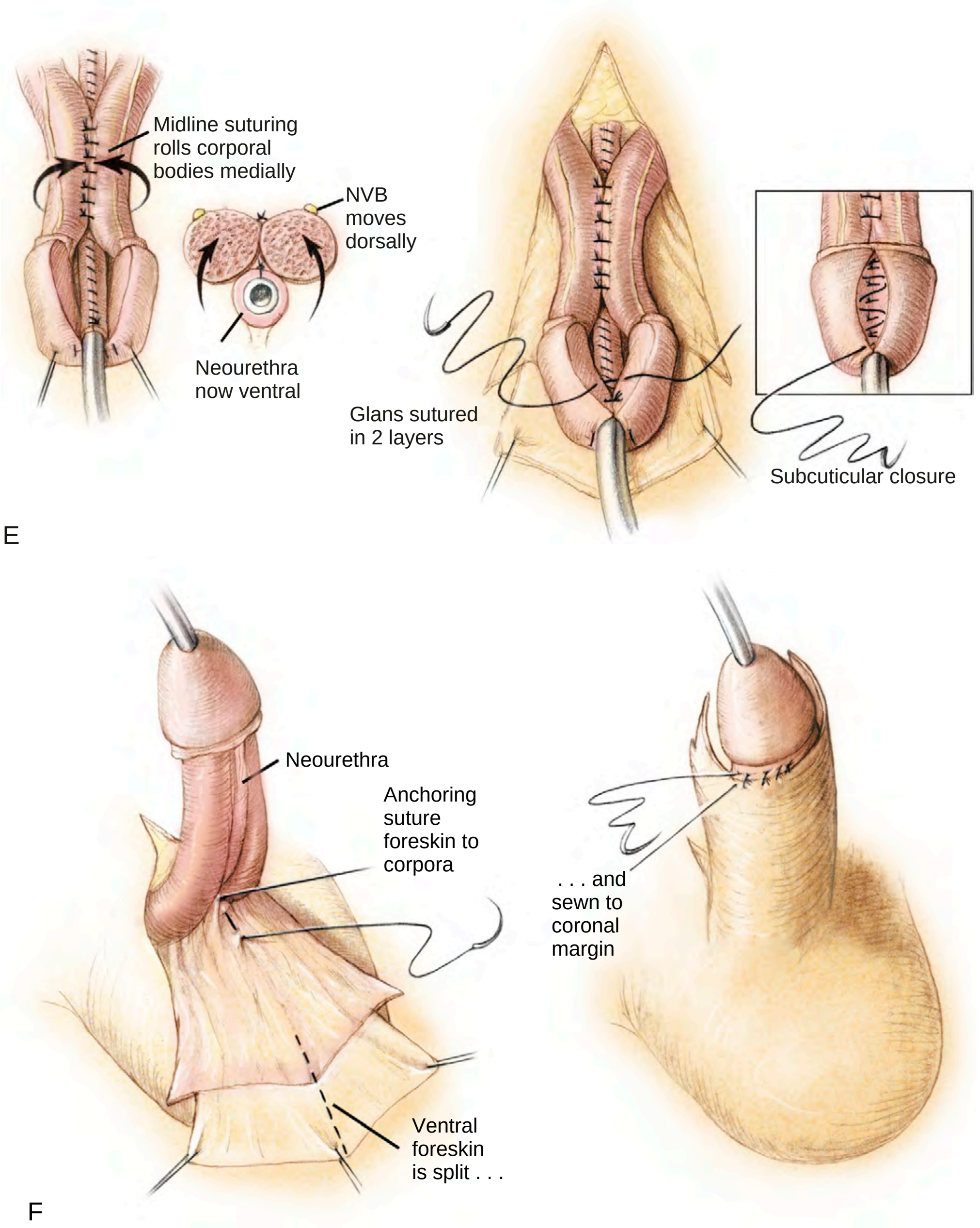

Midline suturing rolls corporal bodies medially
NVB moves dorsally
Neourethra now ventral
Glans sutured in 2 layers
Subcuticular closure
E
Neourethra
Anchoring suture foreskin to corpora
. . . and sewn to coronal margin
Ventral foreskin is split . . .
F

Figure 30-11, cont'd **E,** The corpora are approximated above the urethra to provide an anatomically ventral location of the urethra *(inset)*. The glans is reconstructed in two layers. **F,** A suture is placed at the base of the penis to locate the foreskin on the shaft of the penis and to provide an area of distinction between the penis and scrotum. Foreskin is sewn to the coronal sulcus. (Adapted from Gearhart JP, Mathews R. Exstrophy-epispadias complex. In: Wein AJ et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, chapter 119.)

children who were completely dry after bladder neck reconstruction. Most of these children were 4 to 5 years old and were ready emotionally, maturationally, and intellectually to participate in a postoperative voiding program.

The modified Young-Dees-Leadbetter bladder neck reconstruction[63] and antireflux procedures as performed at our institution are illustrated in Figure 30-12. A very radical dissection of the bladder, bladder neck, and posterior urethra is required, not only within the pelvis but also from the posterior aspect of the pubic bar, to provide enough mobility for the bladder neck reconstruction. This maneuver allows adequate narrowing and tightening of the bladder neck repair and subsequent anterior suspension of the newly created posterior urethra and bladder neck. If visualization of the posterior urethra is problematic, the intrasymphyseal bar can be cut, widening the field of exposure. If the intrasymphyseal bar is cut, mobility of the child should be restricted postoperatively to allow for proper healing.

Postoperative Care

Ureteral stents are placed in the reimplanted ureters and brought out through the wall of the bladder, and the bladder is drained by a suprapubic tube that is left indwelling

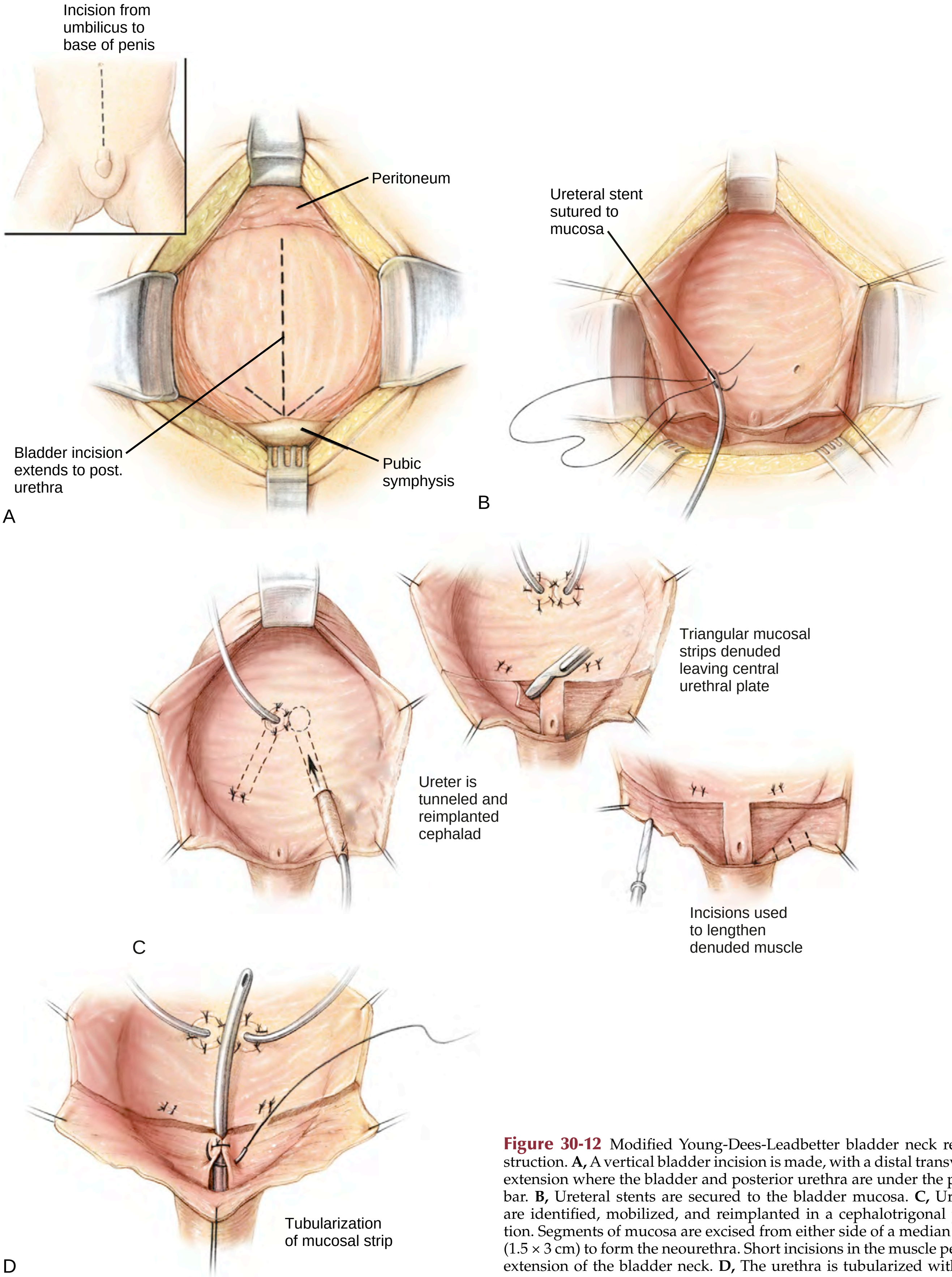
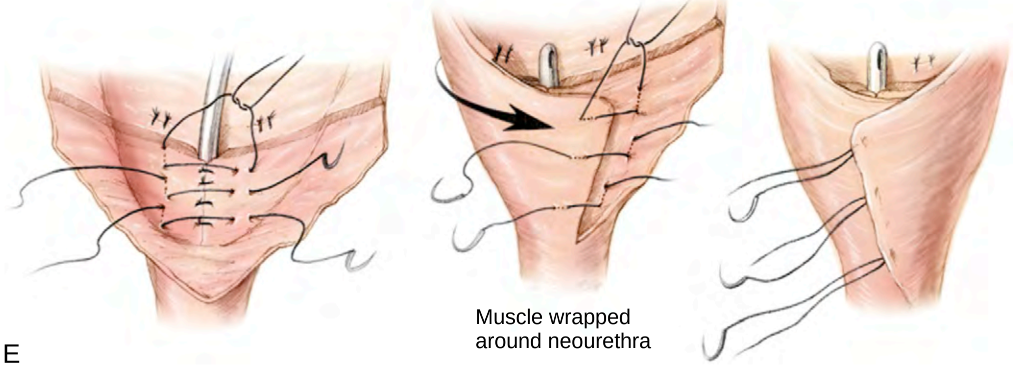

Incision from umbilicus to base of penis
Peritoneum
Bladder incision extends to post. urethra
Pubic symphysis
A
Ureteral stent sutured to mucosa
B
Triangular mucosal strips denuded leaving central urethral plate
Ureter is tunneled and reimplanted cephalad
Incisions used to lengthen denuded muscle
C
Tubularization of mucosal strip
D

Figure 30-12 Modified Young-Dees-Leadbetter bladder neck reconstruction. **A,** A vertical bladder incision is made, with a distal transverse extension where the bladder and posterior urethra are under the pubic bar. **B,** Ureteral stents are secured to the bladder mucosa. **C,** Ureters are identified, mobilized, and reimplanted in a cephalotrigonal position. Segments of mucosa are excised from either side of a median strip (1.5 × 3 cm) to form the neourethra. Short incisions in the muscle permit extension of the bladder neck. **D,** The urethra is tubularized with the use of a continuous running suture.



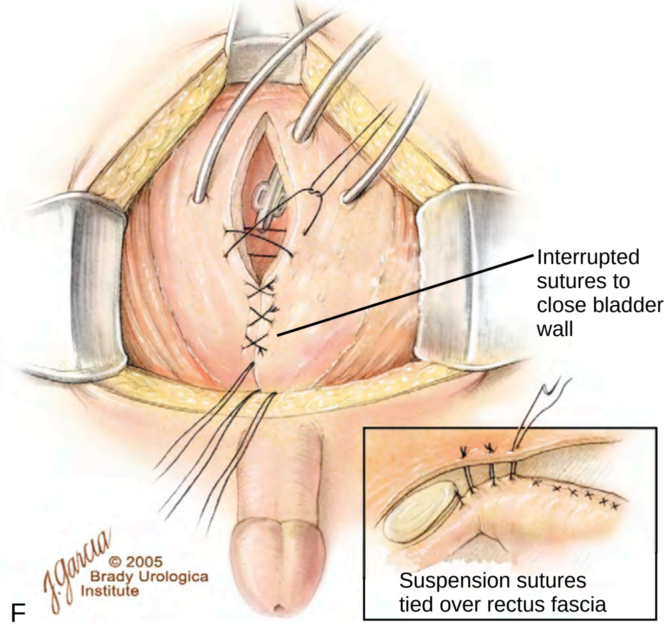

Interrupted sutures to close bladder wall
Suspension sutures tied over rectus fascia
J. Garcia
© 2005 Brady Urologica Institute
F

Figure 30-12, cont'd **E,** The posterior urethra and bladder neck are reconstructed. Bladder muscle is brought together in a double-breasted fashion over the neourethra. **F,** Bladder closure is completed, and the distal suspensory sutures are tied over the abdominal wall *(inset)*. The suprapubic tube and stents are left in place; the urethra is left unstented. (Adapted from Gearhart JP, Mathews R. Exstrophy-epispadias complex. In: Wein AJ et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, chapter 119.)

for 3 weeks. At the end of this period, the suprapubic tube is clamped, and the patient should attempt to void. Initially, the tube should not be clamped for longer than 1 hour. If voiding does not occur, the child is given an anesthetic, and an 8F (2.64-mm) Foley catheter is placed. This is left in place for 5 days; it is then removed, and another voiding trial is begun. This part of the postoperative period is most demanding on the patient, the family, and the surgeon. Some children require several catheter placements before voiding is initiated. After the child can empty the bladder satisfactorily, the suprapubic tube is removed. Frequent bladder and renal ultrasonography is required during the first few months after bladder neck repair.

Combined Bladder Exstrophy and Epispadias Repair in Males

Combined closure of bladder exstrophy and epispadias repair is very similar to the initial portion of the closure of the bladder exstrophy and posterior urethra alone.[47] The urethral plate is examined for its length and depth and for the presence of scarring from a prior attempt at repair. All patients receive preoperative testosterone, and 5% testosterone cream is applied to the urethral plate and bladder neck if prior surgery has produced scarring.

The operative procedure proceeds similarly to a standard closure of the bladder, posterior urethra, and abdominal wall (Fig. 30-13). Special care must be taken to divide any remnants of the urogenital fibers, which are frequently intact in patients who have undergone a failed prior closure. This maneuver allows the vesicourethral unit to be moved posteriorly into the pelvis.

Results of Modern Repair

Bladder, Posterior Urethra, and Abdominal Wall Closure—Results

The definition of a successful bladder exstrophy closure is one that remains intact with proper structural anatomy and ultimately provides proper functioning with adequate storage of urine and ability to void. Several series[64-67] have reported long-term results demonstrating that a successful primary closure is of paramount importance for achieving these goals. Earlier studies by Oesterling and Jeffs[65] in 1987 and by Husmann and colleagues[66] found that the onset of eventual continence was quicker and the continence rate was higher in those patients whose first procedure was successful, with or without osteotomy. Gearhart and colleagues' report[67] in 1996 demonstrated that, among those patients undergoing two attempts, 60% had an adequate bladder capacity for closure, and only 30% ultimately became continent. With three closures, these numbers fell to 40% and 20%, respectively.

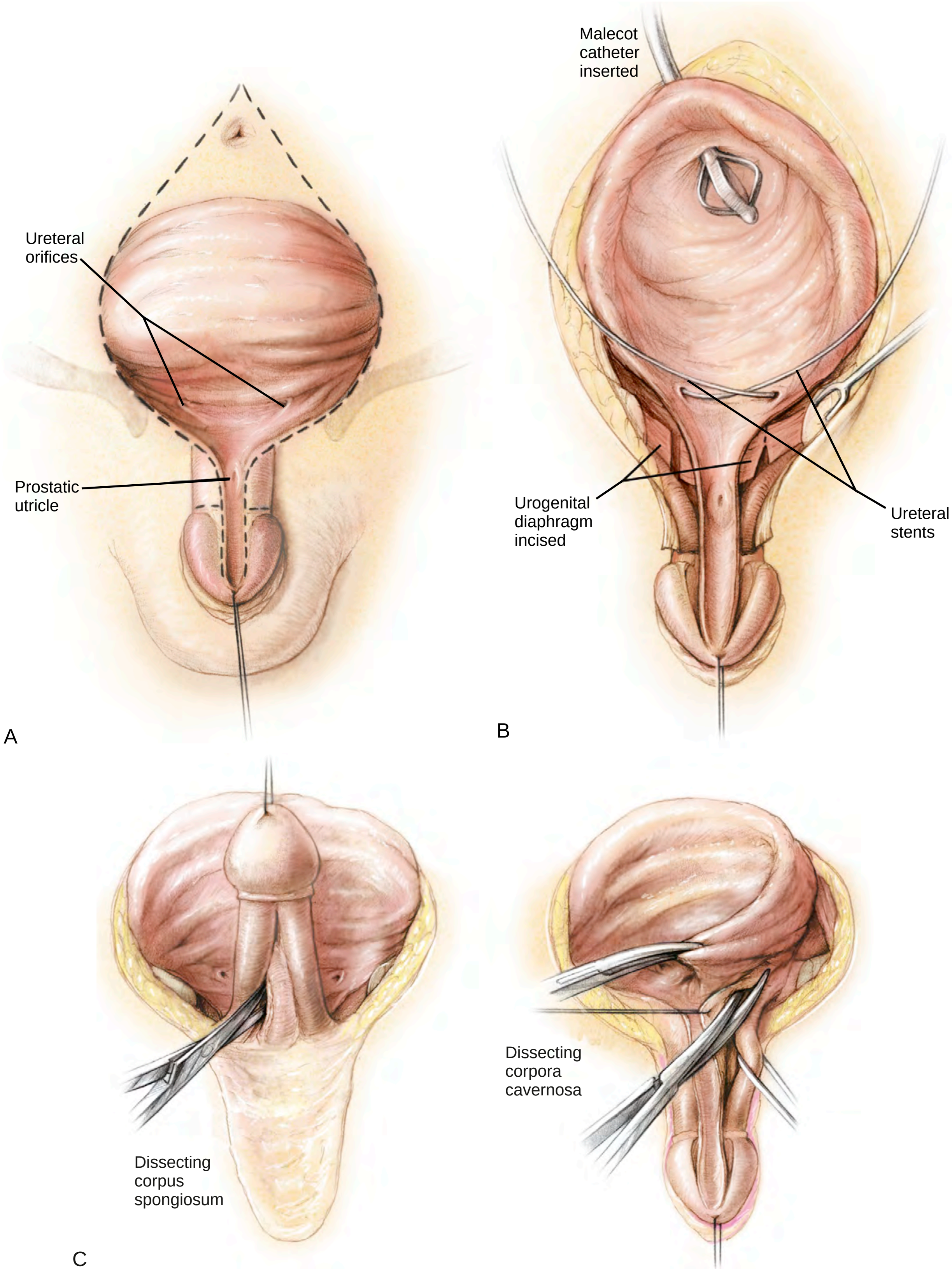

Malecot
catheter
inserted
Ureteral
orifices
Prostatic
utricle
Urogenital
diaphragm
incised
Ureteral
stents
A
B
Dissecting
corpora
cavernosa
Dissecting
corpus
spongiosum
C

Figure 30-13 Combined bladder closure and epispadias repair. **A,** The initial incision extends around bladder and includes the urethral plate. **B,** Stents are placed in the ureters, and a suprapubic tube is placed. Urogenital fibers are divided. **C,** The corpus spongiosum is dissected, leaving a ventral vascularized pedicle. The corpora are dissected proximally toward the bladder.

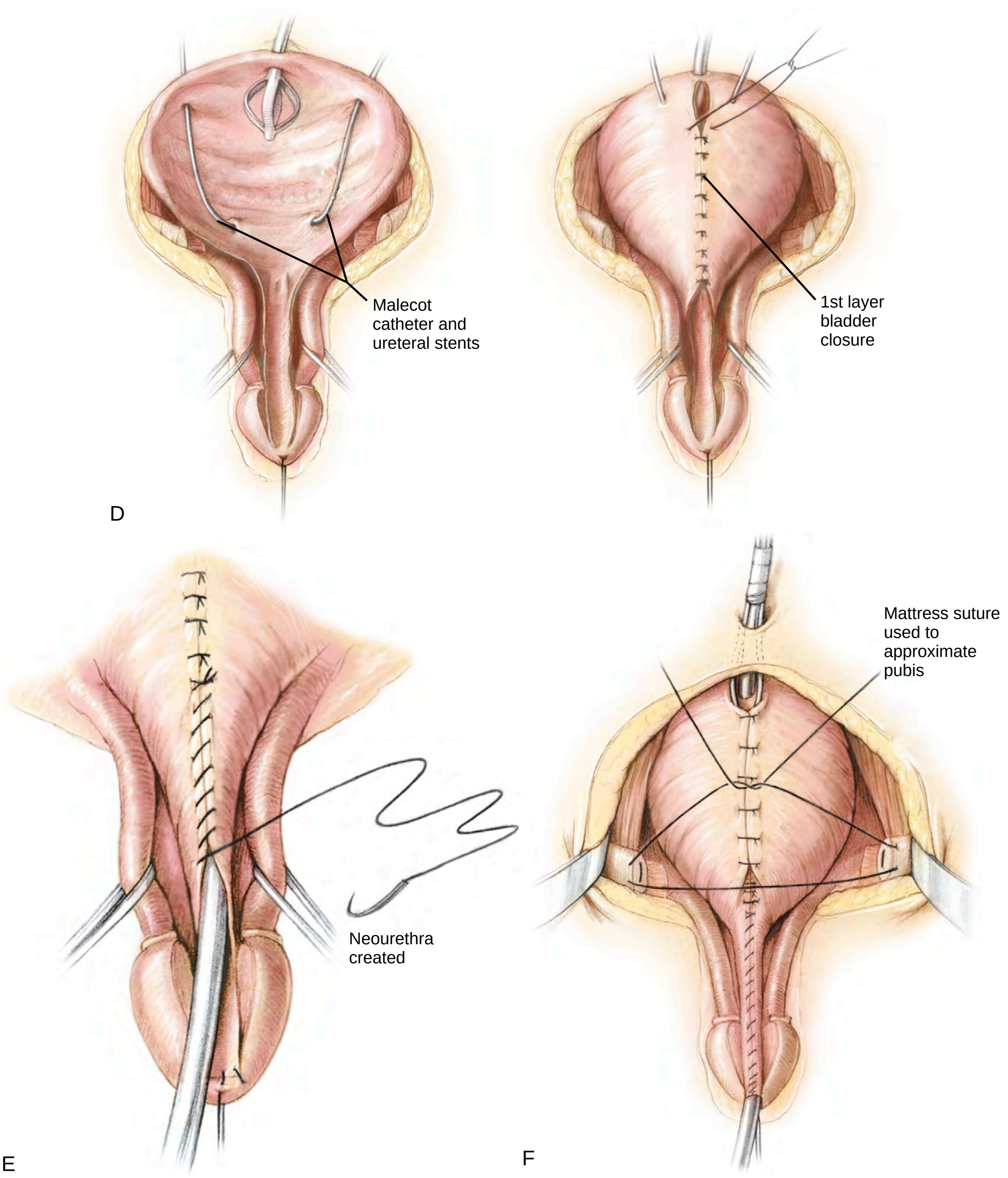
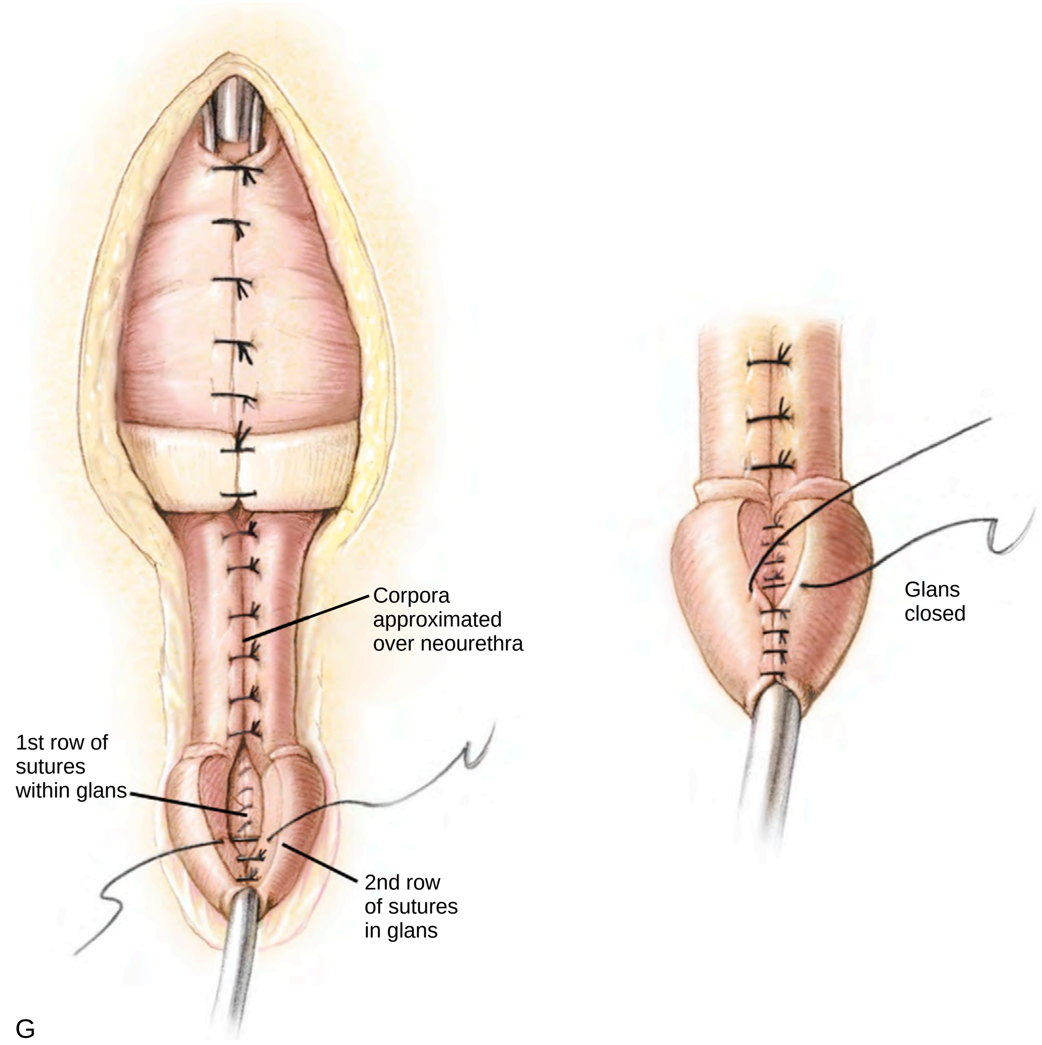
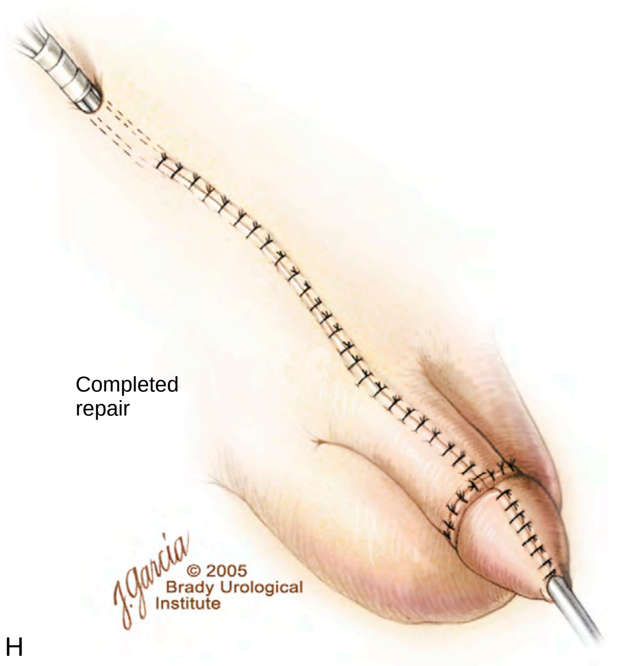

Malecot
catheter and
ureteral stents
1st layer
bladder
closure
D
Neourethra
created
Mattress suture
used to
approximate
pubis
E
F

Figure 30-13, cont'd **D,** Dissection of the urethral plate and corpora is completed. Bladder closure is completed. **E,** The urethral plate is tubularized with the use of a continuous running suture. **F,** Pubic bones are approximated.


Corpora approximated over neourethra
1st row of sutures within glans
2nd row of sutures in glans
Glans closed
G


Completed repair
J. Garcia
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H

Figure 30-13, cont'd **G,** The initial layer of abdominal wall closure is completed, and the corpora are closed over the urethral closure (see Cantwell-Ransley repair). Glans closure is then completed. **H,** Completed penile and abdominal wall skin closure. The urethral stent is omitted in children having initial closure but is left in place in those undergoing reclosure. (Adapted from Gearhart JP, Mathews R. Exstrophy-epispadias complex. In: Wein AJ et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, chapter 119.)

Osteotomy appears to increase the chances for successful surgery, which depends on a secure abdominal wall, posterior urethra, and bladder closure. In the series of 23 patients with multiple failures,[67] 19 had had no form of osteotomy at the time of initial repair. Nelson and associates[68] reported on 56 patients with failed exstrophy closure after at least one prior attempt at osteotomy. They found that repeat osteotomy resulted in few orthopedic complications, and 95% of the patients had a normal gait postoperatively.

Finally, the timing of the initial closure affects outcome, with earlier reconstruction producing better results. Husmann and colleagues[66] reported that patients who had closure before 1 year of age required augmentation only 10% of the time, whereas those who underwent closure after 1 year experienced a 40% augmentation rate. It should be noted, however, that delaying closure to allow for adequate growth of the bladder template does have an important clinical role. Dodson and coworkers,[42] for example, found that they could achieve a continence rate of 47% without augmentation or bladder replacement. Although this figure does not rival series with optimal conditions, it may be the best choice for patients who are not born with optimal parameters.

Epispadias Repair—Results

Anxiety about inadequate, unattractive genitalia still poses the greatest concern to male patients.[69] Modern penile reconstructive techniques should create a straight, functional penis with a glandular meatus and an easily catheterizable neourethral channel, if needed, as well as an acceptable cosmetic result. Many adolescents are dissatisfied by their decreased length; however, no modern technique to our knowledge produces a true increase in penile length, even with complete disassembly or free grafts.

Evolution of penile reconstruction at our institution has continued. In 1994, we modified the Cantwell-Ransley repair by detaching the mucosal plate from the corpora except for the distal 0.5 to 1 cm of the plate (see Fig. 30-11C).

Outcomes from our institution have been reported for 93 patients (79 with classic exstrophy, 14 with epispadias) who underwent primary (77 patients) or secondary (16 patients) repair.[54] At a mean follow-up of 68 months, 87 patients (93%) had a horizontal- or downward-angled penis, whereas 6 (7%) required further straightening operations. The rate of fistula formation was 23% immediately and 19% at 3 months postoperatively. Seven patients developed stricture, and 5 required minor procedures for dorsal skin closure. All of the 77 children who have had cystoscopy demonstrated easily negotiated neourethral channels. Ten of 12 patients older than 16 years have engaged in intercourse and reported satisfaction with cosmesis and function. Kajbafzadeh and colleagues[70] reported their experience with 95 patients and found a stricture rate of only 5% and a fistula rate of 4%. Their revision rate of 16% included minor skin procedures with or without repair of fistula or stricture.

In 1996, Mitchell and Bagley[56] introduced the penile disassembly technique and reported on 10 patients who underwent the procedure. All of their patients had good cosmetic results. Although two patients developed fistulas (one patient had two), these were repeat surgeries for prior failure. A multicenter report[71] on the use of this repair in 17 boys included 3 instances of fistula, 2 of which healed spontaneously, and 1 complete wound dehiscence. Hammouda's series[72] of 42 patients included no fistulas or strictures, but he did report 5 cases in which significant ischemic changes of the glans were noted. In addition to revisions required for fistula, the penile disassembly technique commonly results in a hypospadiac penis that requires subsequent repair.

Bladder Neck Reconstruction—Results

When reporting outcomes from bladder neck repair, our group categorizes patients as spontaneously voiding or performing intermittent catheterization and assigns them to one of three groups: (1) completely dry day and night; (2) social continence, being dry at least 3 hours during the day with occasional nighttime wetting; and (3) wet, being dry for less than 3 hours during the day and wet at night. An analysis of the records of 67 patients who had undergone all phases of bladder exstrophy repair at our institution between 1988 and 2004 and had at least 5 years of follow-up was reported in 2006.[73] All were males, with an average age at closure of 8 days and a mean age at bladder neck reconstruction of 4.8 years. Median bladder capacity at the time of bladder neck reconstruction was 98 mL. Of these 67 patients, 46 (70%) were continent and voiding urethrally without the need for augmentation or clean intermittent catheterization. Seven patients (10%) were socially continent. Six patients required continent diversion for continence after failed bladder neck repair, and seven were wet. Surveillance intravenous pyelograms and ultrasonography discovered only one patient with upper tract abnormalities, which resolved with time.

No major complications were reported in this series, but 18 patients required placement of a urethral catheter, and 12 patients required longer suprapubic tube placement for bladder outlet obstruction. Of note, continence rates were better for children who underwent initial bladder closure before 72 hours of age or after 72 hours with an osteotomy. This result supports the findings of Husmann and colleagues,[66] who reported that only 10% of patients with delayed closure and no osteotomy were continent. Also, those with bladder capacity greater than 100 mL at the time of bladder neck repair became dry earlier in the postoperative period.

Several groups have reported on their experience with staged reconstruction over the past several years. Shaw and coworkers[74] from Indiana reported that 90% of their 48 patients achieved continence, 8% achieved partial continence (defined as dry 1 to 3 hours during the day with minor stress incontinence and occasional nighttime wetness), and 2% remained incontinent. Among the 33 patients who required augmentation, 91% became continent, with 93% requiring clean intermittent catheterization. A meticulous long-term account of 80 patients undergoing the Mollard bladder neck repair was published by Mouriquand and associates[75] in 2003. They found a lower continence rate of 45%, with 48% requiring further surgery and 51% needing endoscopic intervention for late urinary retention. Postoperative complications included recurrent urinary tract infections, dilation of the upper tracts, urinary stones, and bladder perforation. As well as any other, this study demonstrates the importance of early primary closure, performance of penile reconstruction before bladder neck repair, and adequate bladder capacity. The group from Toronto[76] reviewed their outcomes for 43 exstrophy patients divided into three groups: (1) 9 patients who had bladder neck reconstruction as their only incontinence procedure; (2) 15 patients who underwent bladder neck reconstruction with augmentation or appendicovesicostomy or both; and (3) 19 patients with bladder neck closure and appendicovesicostomy. The overall continence rate was 79%, including 56% of group 1, 67% of group 2, and 100% of group 3.

These studies illustrate the results that can be expected with modern staged reconstruction of bladder exstrophy. It is important to note that in all of these experienced groups, there has been evolution of management over the time intervals during which data was collected.

Combined Closure—Results

At the Johns Hopkins Hospital, the combination of bladder closure with epispadias repair has been used predominantly in boys who have already had a failed initial closure or patients in whom closure has been delayed for 5 to 6 months.[77] Results from 33 reclosures and 5 delayed closures have been presented, although the data from the delayed closures is still early, with 3 of the patients awaiting adequate bladder growth. Of the 33 reclosures, 19 (57%) have progressed to bladder neck reconstruction and 12 of these 19 demonstrated at least social continence without the need for intermittent catheterization. Fourteen patients did not undergo bladder neck reconstruction because 3 were dry after bladder closure and epispadias repair, 3 underwent diversion for failure to develop adequate bladder capacity, and 8 are still awaiting bladder growth. Ureteral reimplantation was performed in 22 (66%) of the 33 patients for persistent hydronephrosis, vesicoureteral reflux, recurrent urinary tract infections, or some combination of these conditions. Nineteen patients required further endoscopic procedures or surgery of the bladder neck, penis, or urethra, including 10 for urethrocutaneous fistula and 4 for stricture. Overall, the data suggest that a combination procedure as a means for reclosure yields a continence rate of 50% at best, with significant need for subsequent procedures.

The modern concept of combined bladder closure and epispadias repair in the neonate, or "complete primary repair," was introduced by Mitchell[38,78] in the 1990s, and several groups have now reported on their experience. A comparison of staged reconstruction versus complete primary repair was performed by the group at Boston Children's Hospital[79] to investigate the impact of surgical technique on bladder development. The 23 patients who underwent complete primary repair demonstrated similar bladder capacities to those undergoing staged repair, but the bladders appeared to have a more normal compliance. Bladder instability was commonly seen after staged repair (46% in this series) but was nonexistent in the group undergoing complete repair. However, 70% still required an outlet procedure for dryness. Recent data from Gearhart and associates[80] described 14 patients who had undergone successful complete primary closure of exstrophy in infancy and were then referred for incontinence. Several had "dry intervals" for 1 to 2 hours but continued to leak urine and, therefore, required bladder neck repair.

Complications and failures after complete primary repair are similar to those seen with modern versions of staged repair, with some caveats.[81] Hydronephrosis with vesicoureteral reflux has been reported in 63%[82] to 74%[83] of patients after complete primary repair. Management has usually consisted of performing a subsequent antireflux procedure. Therefore, these authors and others[84] now recommend performing ureteral reimplantation at the time of the initial closure.

Most of the unique complications are associated with the use of the complete penile disassembly technique during complete primary closure. Hypospadias occurred in 77% of the children at Boston Children's Hospital[83] and in 59% of those in an Egyptian series.[82] A multi-institutional study by Alpert and associates raised the concern for development of bladder neck fistulas, which occurred in 41% of their 22 patients.[85] All of the fistulas occurred in males, and most required surgical repair.

Husmann and Gearhart[86] reported several cases of ischemic penile injuries in patients who were referred after undergoing the penile disassembly technique as part of the complete primary repair of bladder exstrophy. These patients experienced loss of the hemiglans, corporal bodies, and urethra in varying combinations and degrees. Ongoing studies are required to elucidate the true incidence of these complications.

Other Techniques

Not all children with bladder exstrophy are candidates for bladder closure, because of a small bladder plate or significant hydronephrosis. Additional reasons for seeking other methods of treatment include failed initial closure with a small remaining bladder and failure of continence surgery. Excluding those patients for whom initial treatment fails, this discussion deals with options available if closure is not chosen or for other reasons has not been suitable.

Ureterosigmoidostomy

Whichever urinary diversion is chosen, the upper tracts and renal function are initially normal. This allows reimplantation of normal-sized ureters in a reliable, nonrefluxing manner into the colon or other suitable reservoir. Ureterosigmoidostomy has been associated with multiple metabolic problems,[87] pyelonephritis, and rectal incontinence secondary to pelvic floor anomalies.[88] The Mainz group employs a rectosigmoid pouch technique that has demonstrated acceptable continence rates and renal preservation in follow-up of greater than 10 years.[41,89] They found that metabolic acidosis requiring alkali supplementation was common but rarely led to significant clinical complications. However, this form of diversion should not be offered until one is certain that anal continence is normal and the family is aware of the potential for serious complications, including pyelonephritis, hyperkalemic acidosis, rectal incontinence, ureteral obstruction, and delayed development of malignancy.[90-92] Surveillance for malignancy in these patients should be initiated 10 years after performance of the ureterosigmoidostomy.

Continent Diversion in the Exstrophy Patient

Indications for continent diversion in exstrophy patients include failure to achieve adequate bladder capacity for bladder neck reconstruction, failure of the bladder to develop adequately after reconstruction, and continued incontinence after proper reconstruction. In a review of 91 patients at our institution, the most common techniques for augmentation and continent diversion were ileocystoplasty or sigmoid cystoplasty with a Mitrofanoff procedure using the appendix, tapered ileum, or ureter.[93] Bladder neck transection was performed in 59 (65%) of patients. Continence was achieved in 93%, with emptying performed via clean intermittent catheterization. The most common complications were bladder stone formation in 24 (26%) of the patients and stomal stenosis in 21 (23%).

For a young child in whom the bladder is too small to close or in the case of a failed closure in which the bladder template is too small to reclose, a nonrefluxing colon conduit may be the best option. This protects the kidneys from vesicoureteral reflux, and undiversion can be performed at an older age.

Sexual Function and Fertility in the Exstrophy Patient

Reconstruction of the male genitalia and preservation of fertility were not primary objectives in early surgical management of bladder exstrophy. Sporadic accounts of pregnancy or the initiation of pregnancy in partners of males with bladder exstrophy have been reported. In two large exstrophy series, male fertility was rarely documented. Only 3 of 68 men in one series[94] and 4 of 72 men in another[95] had successfully fathered children. In a large 1984 study of 2500 exstrophy and epispadias patients that Shapiro and colleagues identified, only 38 had fathered children.[96]

In 1972, Hanna and Williams[97] compared semen analyses in men who had undergone primary bladder closure and ureterosigmoidostomy. A normal sperm count was found in only one of eight men after functional closure and in four of eight men with diversion. Retrograde ejaculation may also account for low sperm counts observed after functional bladder closure. In a long-term study reported from Johns Hopkins in 1996 by Ben-Chaim and associates,[98] 10 of 16 men reported that they could ejaculate a few cubic centimeters of semen, 3 reported that they could ejaculate only a few drops, and 3 reported no ejaculation. Semen analysis was performed in four patients; three had azoospermia, and one had severe oligospermia. The average semen volume of those patients who had sperm counts was 0.4 mL.

In a large German series by Stein and colleagues[99] reported in 1994, the authors found that none of the male patients who had reconstruction of the external genitalia could ejaculate normally, nor had they fathered children. Five patients who did not undergo reconstruction had normal ejaculation, and two had fathered children. Their conclusion was that male patients with genital reconstruction and closure of the urethra demonstrate a high risk of infertility. Assisted reproductive techniques have been applied to the male exstrophy population. In 1993, Bastuba and coworkers[100] reported incidences in which assisted reproductive techniques were used and impregnation was achieved. Currently, therefore, regardless of the method of reconstruction of the external male genitalia, new assisted reproductive techniques will likely allow these patients to achieve fertility.[101]

Sexual function and libido in male exstrophy patients are normal.[102] The erectile mechanism in patients who have undergone epispadias repair appears intact, because 87% of boys and young men in the Hopkins series had experienced erections after the repair of epispadias.[103] Complete absence of ejaculation is rare, although the emission that does occur may be slow and may occur over several hours. In papers from both Woodhouse[102] and Ben-Chaim and associates,[98] most patients reported satisfactory orgasm, and half of the men and all of the women described intimate relationships as serious and long term. Overall, it seems from these papers that most men with exstrophy achieve erection and have a reasonable sex life, and women usually do even better.

Further reconstruction of the female external genitalia can be performed during the adolescent years. In our institution, the external genitalia are fully reconstructed at the time of initial exstrophy closure, because, with the use of the osteotomy, a nice mons can be created and the bifid clitoris can easily be brought together at the midline. Occasionally, vulvoplasty has to be performed before patients can become sexually active. In Woodhouse's experience,[104] most patients required vaginoplasty for intercourse to take place. He reported normal intercourse in all of his female patients, but three found it painful. At Johns Hopkins, several patients were seen who had not had vulvoplasty and had two clitoral halves; they had a normal sex life with normal orgasm and had no desire for repair.

Monsplasty is very important,[61] either in infancy or in adolescence, because hair-bearing skin and fat need to cover the midline defect. As mentioned earlier, we believe that this should be done at the initial closure, but it certainly can be done during adolescent life with the use of rhomboid flaps, as popularized by Kramer and Jackson.[105] Stein and associates[106] reviewed a large German series of female exstrophy patients in 1995 and found that a cut-back vaginoplasty was required before intercourse in 23 patients.

Obstetric and Gynecologic Implications

With the improvement of bladder exstrophy management over the past half century, more women with exstrophy are surviving to their reproductive years and are confronted with the challenge of conceiving and bearing children.[107] In one of the first papers to address the issue of pregnancy in adult exstrophy patients, Clemetson[108] reviewed 65 pregnancies in 46 women from 1924 to 1958. His series noted that (1) premature labor was common, perhaps due to increased incidence of urinary tract infection; (2) a 25% incidence of malpresentation resulted from the contribution of the pelvic floor anomalies to poor anterior support; (3) obstruction from vaginal stenosis precluded vaginal delivery in some cases; and (4) a 50% incidence of uterocervical or vaginal prolapse was seen after vaginal delivery. A subsequent report by Krisiloff and associates[109] found prolapse to be the main complication with pregnancy. Burbige and associates,[110] in 1986, described 40 women, ranging in age from 19 to 36 years, who had been treated in infancy for bladder exstrophy. Fourteen pregnancies in 11 women had resulted in 9 normal deliveries, 3 spontaneous abortions, and 2 elective abortions. Uterine prolapse occurred in 7 of 11 patients during pregnancy, all of whom had undergone prior urinary diversion. In their series, women who had undergone prior urinary diversion were delivered vaginally, whereas those with functional bladder closures received cesarean sections to eliminate stress on the pelvic floor and avoid traumatic injury to the urinary sphincter mechanism.[110] With modern reconstructive techniques, successful pregnancies have been reported in female patients after continent urinary diversions.[111]

A review[112] of urogynecologic issues in 83 women with the exstrophy-epispadias complex revealed a 73% incidence of urinary tract infections, and those women with classic bladder exstrophy had an 18% incidence of pelvic organ prolapse, with a mean age at onset of 16 years. Besides the risk of pregnancy, Stein and associates found that, after vaginoplasty, 17% of women developed organ prolapse within months of the procedure.[106] Pelvic organ prolapse in the female exstrophy patient is likely due to the wide, flat levator ani muscles, which are anteriorly placed, and the fact that the cervix is close to the pelvic floor. There is a wide levator hiatus, which may be widened further after vaginoplasty or childbirth. Perhaps with widespread application of pelvic osteotomy and better closure of the pelvic floor, the incidence of uterine prolapse will decrease in the future.

Regardless of the method of repair, the uterus must be anchored in such a way that it is solidly fixated in the pelvis and less prone to prolapse. Woodhouse,[104] believed that anterior fixation is insufficient in the exstrophy patient once prolapse occurs. Muir and colleagues[113] suggested that an abdominal sacral colpopexy may be more durable in the exstrophy patient population.

Long-Term Psychosocial Issues

Since the late 1990s, interest in long-term adjustment issues in patients with bladder exstrophy has increased. Children with exstrophy undergo multiple reconstructive surgeries and have potential problems with respect to urinary incontinence and sexual dysfunction. Reiner and Gearhart[114] evaluated 20 exstrophy patients between the ages of 5 and 22 years and found that 19 of them met criteria (*Diagnostic and Statistical Manual for Mental Disorders*, version IV) for at least one anxiety disorder. However, the ultimate outcome may be better measured by how these children adjust overall in society.

In 1998, Montagnino and coworkers[115] evaluated younger children, who performed more poorly and had disturbed behavior, specifically in skills relating to function in school. Children who achieved continence when older than 5 years of age were more likely to have problems with acting-out behavior. They found no differences in the adjustment of boys versus girls, bladder versus cloacal exstrophy, the type of continence strategy, or gender reassignment versus no reassignment. The conclusion from this long-term study was that children with exstrophy do not have clinical psychopathologic problems, but they do show differences in adaptive and acting-out behavior. With regard to gender differences in coping with exstrophy, Lee and coworkers[116] found, in 122 adolescent patients, that girls had more close friendships, fewer disadvantages in relation to healthy same-gender peers, and more romantic partnerships than boys. Family planning also seemed to be less of a problem in affected females. On the other hand, these researchers did not find patient gender to influence adjustments within school or professional career.

In addition to issues surrounding continence, Meyer and colleagues[117] emphasized body image, self-esteem, sexuality, sexual function, and fertility as areas of concern among adolescent exstrophy patients. They and others[118] advocated focusing on aesthetic aspects of abdominal wall and genital reconstruction, as well as secondary plastic procedures.

Reiner[119] studied 42 children with exstrophy and presented preliminary results suggesting that these patients tend to have more behavioral and developmental problems than children with other abnormalities. Although these problems were not severe, he recommended intervention in infancy with the patient and the family, continuing with long-term psychiatric support into adulthood. In a European study reported in 1994, Feitz and associates[120] found a more positive picture when they evaluated 11 men and 11 women with exstrophy; 91% of the men and 82% of the women did not have clinical levels of psychological stress. The authors concluded that the patients had a positive attitude toward life. Continued support as these patients age is likely to be advantageous; as a study by Ebert and coworkers[121] discovered, 93.9% of adolescents expressed some interest in psychological assistance.

EPISPADIAS

Epispadias is the least severe form of the exstrophy-epispadias complex but still represents a major clinical problem and management challenge. It consists of a dorsally located ectopic meatus that results from nonclosure of the urethral plate, often extended to the level of the bladder neck. This is a rare entity, with an estimated incidence of 1 in 117,000 males and 1 in 484,000 females.[37]

Embryologically, epispadias occurs when there is defective migration of the primordium of the genital tubercles as it moves toward the midline superior to the cloacal membrane to form the genital tubercle at approximately the 5th week of gestation. The result is a defect in the dorsal wall of the urethra. Instead of the normal urethra, the nontubularized urethral plate overlies the dorsum of the corpora cavernosa. Urinary incontinence is the result in the more severe forms when the bladder neck is involved.

There is a characteristic widening of the pubic symphysis secondary to outward rotation of the innominate bones. However, the diastasis is minimal and rarely requires osteotomy for pelvic reconstruction.

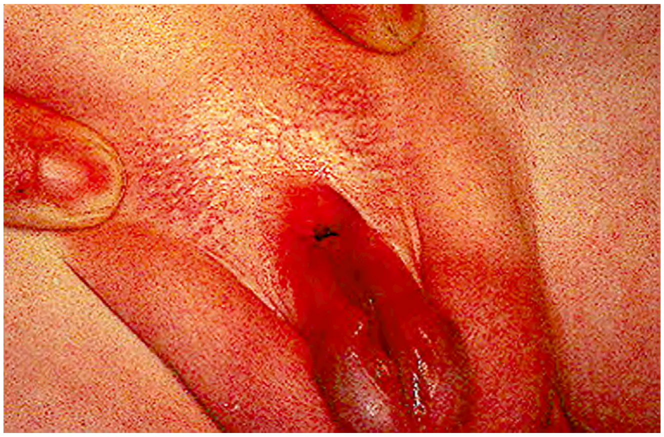

Figure 30-14 Male with penopubic epispadias.

Male Epispadias

In males, the dorsal meatus may be found on the glans, penile shaft, or penopubic region, and all types are associated with varying degrees of dorsal chordee. Urinary continence is directly related to the severity of the deformity. The most common form of male epispadias is the penopubic subtype (Fig. 30-14), followed by the intermediate form with the meatus on the penile shaft; the rarest type is the glandular variant. Kramer and Kelalis[122] reviewed their experience with 82 male patients and found 49 penopubic cases, 21 penile variants, and 12 patients with the glandular form.

The penopubic or complete epispadias defect involves the entire urethral plate, beginning at the bladder neck, and includes a cleft striated sphincter. Lack of a congenital continence mechanism results in a thin-walled bladder with poor capacity. A small gap is seen between the two pubic bones, but the symphysis is dense and fibrous, and the pelvic ring is completely closed. Vesicoureteral reflux occurs in 30% to 85% of the patients in some series,[122-124] which is significantly lower than the 100% incidence seen in classic exstrophy patients. Inguinal hernias occur at a relatively high rate, 33% in the series from Johns Hopkins,[125] but again this is much lower than in the classic exstrophy population.

Intermediate forms of epispadias involve an intact bladder neck, so incontinence is not usually a problem. Corporal malrotation and dorsal chordee are present and must be addressed at the time of reconstructive surgery. The glandular presentation is somewhat more subtle in that the foreskin may be intact. In these patients, the penis is commonly shorter than normal, and chordee may be obvious only during erections. Therefore, the surgeon should investigate via production of an artificial erection at the time of repair and address the situation accordingly.

Surgical Management

Reconstructive surgery aims to create a functional and cosmetically acceptable phallus and to achieve urinary continence with renal preservation. Surgical management is virtually identical to that for closed bladder exstrophy.

The modified Cantwell-Ransley procedure and the complete disassembly technique (both described earlier in this chapter) are two methods used to reconstruct complete epispadias. There is little disagreement that epispadias repair and bladder neck reconstruction may be combined in selected patients when bladder capacity is good. Bladder capacity increases as a direct result of the higher outlet resistance after urethroplasty. Ben-Chaim and associates[125] found an average increase of

42 mL in bladder capacity within 18 months after urethroplasty. Those who support the complete penile disassembly technique argue that many of their patients are continent without the need for further bladder neck reconstruction, and in those with a patulous bladder neck, reconstruction can be performed at the time of urethroplasty, obviating a second procedure.[126]

Genital reconstruction involves the release of chordee and division of the suspensory ligaments, dissection of the corpora from their attachments to the inferior pubic ramus, lengthening of the urethral groove, and lengthening of the corpora, if needed, by incision and anastomosis or grafting, or more commonly by medial rotation of the ventral corpora in a more downward direction. The use of a cavernostomy is uncommon, because there is little or no intrinsic deformity of the corpora; medial rotation is almost always sufficient, and mobilization of the neurovascular bundles can be avoided.

In the modified Cantwell-Ransley procedure (see Fig. 30-12), the urethra is completely reconstructed from the urethral plate, which is mobilized on its pedicle, retubularized, and repositioned ventrally. A main point of difference from the Mitchell technique is that the distal 1 cm of the urethral plate is not dissected free from the glans penis. Once the corpora have been rotated medially and glanuloplasty and meatoplasty have been performed, Z-plasty is done at the dorsal base of the penis, to provide adequate skin and to prevent dorsal retractile scarring. Complete penile disassembly[38] depends on the blood supply of the epispadiac penis, which consists of paired dorsal arteries and neurovascular bundles to each hemiglans, deep cavernosal arteries to the corporal bodies, and supply via the spongiosa to the proximal urethral plate. In this case, the three components of the penis, including the two corporal bodies and their respective hemiglans, and the urethral wedge consisting of the urethral plate and underlying spongiosum, are dissected completely free from each other. The hemicorporal bodies can then be rotated medially to correct the chordee, and cavernostomy is never performed.

Results of Epispadias Repair

In epispadias patients, as in those with classic bladder exstrophy, bladder capacity is the single most important indicator of eventual continence.[127] Arap and coworkers[123] found that continence was achieved in 71% of patients with an adequate bladder volume, but in only 20% if the bladder volume was inadequate. Overall, continence rates after staged procedures with bladder neck reconstructions have been very good. In the 1995 Johns Hopkins series,[125] the urinary continence rate was 82%, which is similar to the results obtained in other groups.[122-124] Time to initial continence was 90 days postoperatively, compared to 110 days for bladder exstrophy, and none of the patients required augmentation or self-catheterization. It is likely that these bladders respond better than exstrophied bladders.

Cosmetic results, in terms of a straight or downward-angled penis, and functional results with regard to erectile function have been uniformly excellent in all of the aforementioned series. Mesrobian and colleagues reported a good cosmetic result in 70% of their patients. Within their series, 80% of the men reported satisfactory sexual intercourse, and 19 of the 29 married patients had fathered children.[128] A long-term study by Mollard and coworkers[124] described similar outcomes.

Urethrocutaneous fistulas and urethral strictures represent the most common complications encountered after the modified Cantwell-Ransley procedure. Surer and associates[54] evaluated their patients 3 months postoperatively and found that 19% had developed fistulas and the stricture rate was less than 10%. Ransley and colleagues[53] had a fistula rate of 4% with a stricture rate of 5.3%. Reoperations for fistula, stricture, recurrent chordee, and recurrent incontinence are uncommon but occasionally necessary. In the case of continued incontinence, some surgeons have attempted submucosal injection of bulking agents with varying degrees of success.

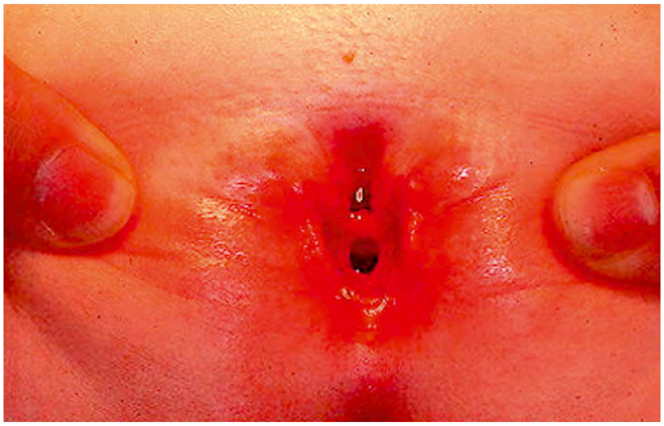

Figure 30-15 Female with complete epispadias.

Outcomes data for the complete penile disassembly technique is not as extensive, given the relative newness of the method. A multicenter study[71] with a total of 17 patients found that 16 had good cosmetic results and were able to achieve straight erections. Grady and Mitchell[38] reported a continence rate approaching 80% and noted that the Leadbetter bladder neck reconstruction was effective in establishing continence after a failed initial procedure. The incidence of fistula was reported in three series to be between 2% to 20%.[38,71,72]

Female Epispadias

As in the male, there are three types of epispadias in the female, based on the severity and location of the defect. Because of the rarity of this malformation and the variance of presentation, these patients are frequently not diagnosed at birth and present at a later age complaining of constant wetness.[129] In the most severe and common form of epispadias (Fig. 30-15), the defect extends along the entire length of the urethra and bladder neck, which cleaves the sphincteric mechanism, rendering the child incontinent. The genitalia are remarkable for the bifid clitoris and a depressed mons that is covered by smooth, glabrous skin. The labia minora are usually poorly developed and terminate anteriorly at the corresponding half of the bifid clitoris, where there may be a rudiment of a preputial fold. As in the male, the pubic symphysis may have a very small gap (compared to that seen in classic exstrophy) which is traversed by a narrow fibrous band.[130]

Previous comments regarding vesicoureteral reflux in male epispadias also apply to females. As in males, ureteral reimplantation is performed at the time of bladder neck reconstruction. We recommend doing this for all patients, because the increased bladder neck resistance may contribute to de novo reflux in patients in whom it is initially absent.

SURGICAL MANAGEMENT

Repair of the epispadias defect in females strives to achieve urinary continence, preserve the upper urinary tract, and create functional and cosmetically acceptable external genitalia. Procedures that merely increase urethral resistance without correcting incontinence or addressing congenital malformation, such as transvaginal plication of the urethra and bladder neck, muscle transplantations, urethra twisting, cauterization

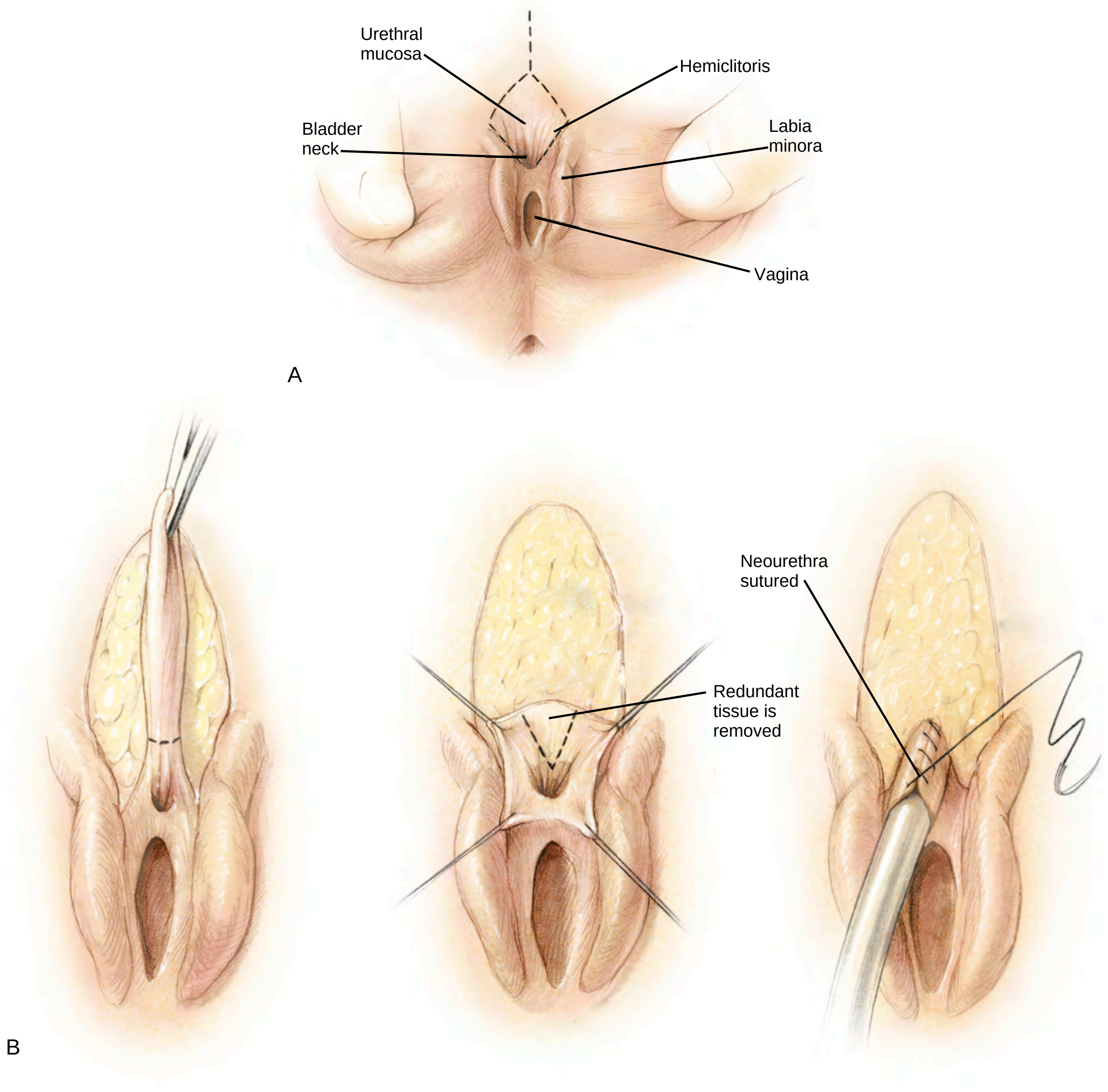

Figure 30-16 **A,** Typical appearance of female epispadias with initial incisions outlined. **B,** Excision of the glabrous skin of the mons. Tapering of the urethra with a dorsal resection of a wedge of tissue. Reconstruction of the urethra over a catheter with a running suture.

of the urethra, bladder flap, and Marshall-Marchetti vesicourethral suspension, have yielded disappointing results.[131-134]

As with males, increasing outlet resistance results in an increase in bladder capacity, so we perform the reconstruction as a staged procedure. Typically, urethral and genital reconstruction is performed at 1 year of age, followed by bladder neck reconstruction when the patient is 4 to 5 years old. This timetable allows adequate bladder development and allows the child to mature enough to participate in a voiding program. Reconstruction of the urethra and external genitalia is performed at the same time (Fig. 30-16). A 10F (3.3-mm) catheter is placed at the end of the procedure. If bladder neck reconstruction is being done concurrently, a small 8F urethral stent is used.

Surgical Results

Urinary continence rates of better than 80% have been reported in several series, with very infrequent need for intermittent catheterization, augmentation, or urinary diversion for failed reconstructions.[130,135,136] All of the patients in the reported series achieved bladder capacities greater than 80 mL. At our institution,[135] the mean capacity after genitourethral reconstruction and at the time of bladder neck reconstruction was

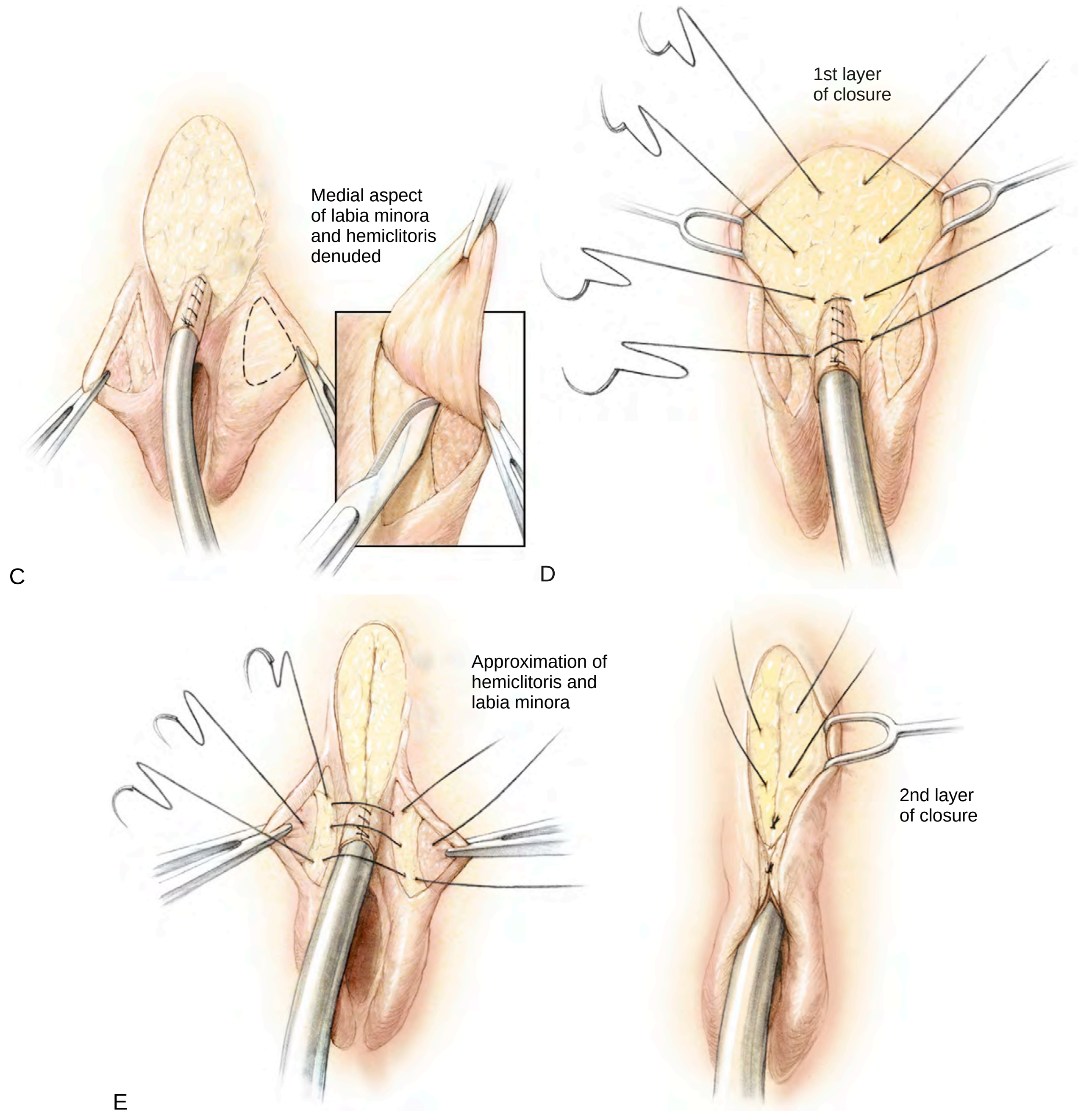

Figure 30-16, cont'd **C,** Denuding of the medial aspect of the labia minora and clitoris. **D,** Initial layer of the mons closure. **E,** Approximation of the labia minora over the urethral reconstruction and second layer of mons closure.

121 mL. We also found that the time interval to achieve continence was 18 months after combined genitourethral and bladder neck reconstruction, compared with 23 months if these procedures were performed in a staged fashion. Kramer and Kelalis[136] found that several of their patients became continent within a short period, whereas other patients took several years to obtain complete continence. They attributed this result to a delay in pelvic muscular development. Although there appears to be an advantage, in terms of interval to dryness, in combining the genitourethral and bladder neck reconstructions, we believe that the increased bladder capacity obtained with the preliminary urethroplasty outweighs this benefit.

CLOACAL EXSTROPHY

Cloacal exstrophy, commonly referred to as the omphalocele, exstrophy of the bladder, imperforate anus, and spinal abnormalities (OEIS) complex[137] in nonurologic literature, represents one of the most severe congenital anomalies compatible with intrauterine viability. It is exceedingly rare, occurring in approximately 1 of every 200,000 to 400,000 live births.[138] Surgical reports[102,139] have indicated a male-to-female ratio of 2:1, but a Spanish population-based study[140] including 1.6 million live births and 10,000 stillbirths found a female preponderance, with a ratio of 0.5:1. The inheritance pattern of cloacal exstrophy is unknown.

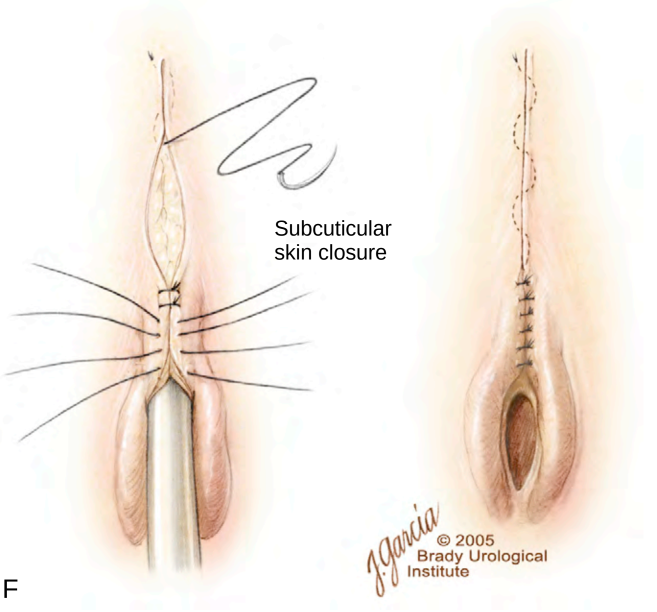

Figure 30-16, cont'd **F,** Creation of a clitoral hood and completion of the mons closure. (Adapted from Gearhart JP, Mathews R. Exstrophy-epispadias complex. In: Wein AJ et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, chapter 119.)

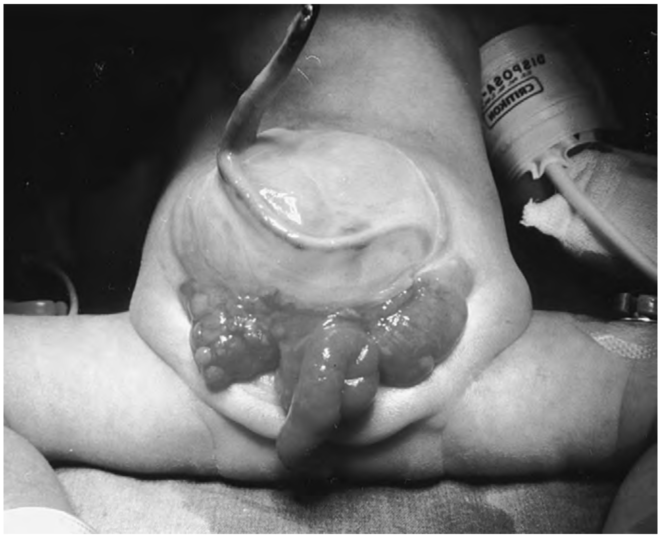

Figure 30-17 Cloacal exstrophy in a newborn male. A large omphalocele with prolapse of the ileum through the ileocecal area between exstrophied hemibladders and a small part of the right hemiphallus are visible.

Embryology and Anatomy

Until the 5th week of gestation, the urinary, genital, and gastrointestinal tracts empty into a common chamber, the cloaca. At approximately the 4th week of development, lateral mesodermal tissue migrates medially between the endoderm, which forms the cloacal membrane, and the overlying ectoderm. By the 6th week, this layer forms the infraumbilical abdominal wall. It is postulated that, if mesodermal invasion does not occur, the infraumbilical cloacal membrane persists, with subsequent poor abdominal wall development, and is therefore prone to rupture.[141] The urorectal septum begins to divide the cloaca into an anterior urogenital sinus and a posterior anorectal canal after the 4th week of gestation, and this septum descends caudally between weeks 6 and 8. If perforation of the anterior cloacal membrane occurs before complete descent of the urorectal septum, the common cloaca will be affected, and cloacal exstrophy will be the result. The anomaly must represent not an arrest in development but, more likely, some form of primary polytopic developmental field defect.[140]

According to Muecke,[142] an abnormally extensive cloacal membrane produces a wedge effect, serving as a mechanical barrier to mesodermal migration, which results in impaired development of the abdominal wall, failure of fusion of the paired genital tubercles, and diastasis pubis. Exstrophy of the cloaca results when the wedge effect occurs before the complete caudal migration of the urorectal septum at 6 weeks.[143]

Ultrasound prenatal imaging data, however, have cast some serious doubt regarding the current thought that inciting events occur between the 6th and 8th week of gestation. Langer[144] and Bruch[145] and their colleagues reported prenatal diagnoses of cloacal exstrophy in fetuses with intact cloacal membranes at 18 to 24 weeks. In 1996, Vermeij-Keers and associates[146] postulated that the embryologic maldevelopment of cloacal exstrophy is caused by poorly orchestrated cellular proliferation and apoptosis, with resultant poor mesodermal malformation from the umbilical ectodermal placode. Rather than debate about the exact timing of the disintegration of the cloacal membrane (8 versus 22 weeks), they describe the urorectal septum, abdominal wall, and cloacal membrane as related, with a similar origin (ectodermal placodes), and an imbalance between cellular proliferation and cell death.

Anatomically, there is exstrophy of the foreshortened hindgut or cecum, which displays its bulging mucosa between the two exstrophied hemibladders (Fig. 30-17). The orifice of the terminal ileum, rudimentary tailgut, and a single appendix are apparent on the surface of the everted cecum. The tailgut is blind ending and is of varying length. The ileum may be prolapsed. The pubic symphysis is widely separated, the hips are externally rotated and abducted, and the phallus is separated into a right and a left half with an adjacent labium or scrotal half. Sponseller and associates described the anatomy of the bony pelvis in the patient with cloacal exstrophy.[11] Using three-dimensional CT scans of these infants, they reported marked external rotation deformities of both the anterior and posterior pelvis. Unlike classic bladder exstrophy, in which there is symmetric shortening of bone in the pubis, there were marked asymmetries in the pubis in patients with the cloacal form. Schlegel and Gearhart[21] defined the neuroanatomy of the pelvis in the child with cloacal exstrophy. The innervation of the hemibladders and corporal bodies arises from a pelvic plexus on the anterior surface of the rectum. The nerves to the hemibladders travel the midline along the posterior inferior surface of the rectum and extend laterally to the hemibladders. Innervation to the duplicated corporal bodies arises from the sacral complex, travels in the midline, perforates the inferior portion of the pelvic floor, and courses medially to the hemibladders.

In a large review by Diamond,[147] associated anomalies were seen in multiple organ systems. The incidence of spina bifida varied from 29% to 75%, including patients with both meningoceles and lipomeningoceles. When spina bifida patients were stratified according to neural involvement, myelomeningocele was noted in 17% to 52% of cases. In the same report, 72% of the myelomeningocele defects were found to be lumbar, 14% sacral, and 14% thoracic.

Upper urinary tract anomalies occurred in 41% to 60% of patients in Diamond's review.[147] The most common anomalies were pelvic kidney and renal agenesis, each occurring in up to one third of patients. Hydronephrosis and hydroureter were common, occurring in one third of patients. Müllerian anomalies, including duplication of the uterus and vagina, were also reported in several patients. The most commonly reported müllerian anomaly was uterine duplication, seen in up to 95% of patients. The vast majority had partial duplication, predominantly a bicornate uterus. Vaginal duplication occurred in 65% of patients, and vaginal agenesis was found in approximately 25% to 50%. There were cases of complete duplication of the uterus and fallopian tubes associated with both vaginal duplication and vaginal agenesis.

Skeletal and limb deformities were reported by Diamond[147] to occur in 12% to 65% of cases. The vast majority of these were clubfoot deformities, although an absence of feet, severe tibia-fibula deformities, and congenital hip dislocations were also commonly noted in this group of patients.

Gastrointestinal tract anomalies occurred in virtually all patients. In Diamond's series, the incidence of omphalocele was 88%, with the majority of all series reporting rates of 95% or greater. Omphaloceles do vary in size and usually contain small bowel or liver or both. Immediate closure of the omphalocele defect in the newborn period is advised to prevent subsequent rupture.

Hurwitz and associates,[138] in their large 1987 review of cloacal exstrophy patients, reported a 46% incidence of associated gastrointestinal tract anomalies, with malrotation, duplication anomalies, and anatomically short bowel occurring with equal frequency. They noted a 23% incidence of short gut syndrome, which is similar to the 25% incidence reported by Diamond.[147] It now seems well accepted that short gut syndrome may occur in the presence of normal small bowel length, suggesting absorptive dysfunction and emphasizing the absolute need to preserve as much large bowel as possible.[148]

Prenatal Diagnosis

Since the use of ultrasonography for prenatal diagnosis of cloacal exstrophy was initially described in the early 1980s, further refinements have occurred.[139,149] Chitrit and coworkers[149] reported in 1993 the diagnosis of monozygotic twins with cloacal exstrophy detected during antenatal ultrasound scanning. Since then, there have been only occasional case reports of the prenatal diagnosis of cloacal exstrophy, and only 15% of patients with this abnormality have been diagnosed prenatally and reported in the literature. With the marked improvements in survival since the 1980s, the importance of early diagnosis has increased.

In 1998, Austin and associates[150] reviewed 22 patients with this abnormality and proposed major and minor criteria for the prenatal diagnosis of cloacal exstrophy. Criteria for establishing the diagnosis were categorized as major or minor based on the frequency of occurrence and were not related to severity. Parameters were considered major if they occurred more than 50% of the time. Gestational age for the diagnosis of cloacal exstrophy ranged from 15 to 32 weeks, with a mean of 22 weeks. Major diagnostic criteria include nonvisualization of the bladder in 91%, a large midline infraumbilical anterior wall defect or cystic anterior wall structure in 82%, an omphalocele in 77%, and a myelomeningocele in 69%. Minor criteria included lower extremity defects in 23%, renal anomalies in 23%, ascites in 14%, widened pubic arches in 18%, a narrow thorax in 9%, hydrocephalus in 9%, and a single umbilical artery in 9%.

Della Monica and associates used the "elephant trunk–like" prolapsed terminal ileum image to diagnose a case of cloacal exstrophy in a fetus at 22 weeks of gestation. This finding should be added to the list of criteria for the prenatal diagnosis of cloacal exstrophy.[151,152]

Surgical Management

Immediate management is directed to the medical stabilization of the infant. Evaluation and appropriate management of associated malformations should be undertaken. In infants with few other associated malformations who are medically stable, both bladder and omphalocele closure should be considered. Bladder and bowel should be moistened with saline solution and covered with a protective plastic dressing. Evaluation of the genitalia and gender assignment should be made by a gender assignment team, including a pediatric urologist, pediatric general surgeon, general pediatrician, pediatric endocrinologist, and psychiatrist familiar with ambiguous genitalia. Consultation from the social work service, pediatric orthopedic surgical staff, and other relevant professionals should also be obtained. In a large medical center with experience in dealing with these patients, these multiple consultations can be accomplished in a short period. In those patients with acute medical issues, delayed closure after gastrointestinal diversion is appropriate.[153]

Gender Assignment

Gender assignment decisions are limited to the genetic male patient with cloacal exstrophy. Male gender assignment is certainly appropriate for boys with adequate bilateral or unilateral phallic structures. One of the most controversial issues in pediatric urology concerns the genetic male patient who does not have adequate phallic structures. A survey by Diamond and associates[154] questioned 185 pediatric urologists about their management preferences for these patients. The two thirds majority who favored male assignment voiced concerns about testosterone imprinting on the brain during fetal and early infantile development. They also interpreted the available data to indicate that patients raised male had better outcomes. A desire to avoid gonadectomy in very young patients and optimism about future fertility with assisted reproductive technology were important factors as well. The minority position of assigning female gender was supported by older and more experienced practitioners who cited the difficulty in creating functional male genitalia and the high success rates of surgical creation of female genitalia. Their interpretation of available data was that patients raised as females do better with respect to gender identity and psychosocial development.

In a review of 14 genetic male cloacal exstrophy patients reconstructed and raised as female, Reiner and Gearhart[155] reported some disappointing results. Whereas 5 of the patients adjusted well to being female, 8 had declared themselves male, and 1 adamantly refuses to discuss the issue. They conclude that clinical interventions for these neonates should be reconsidered in light of their findings. Meyer-Bahlberg[156] provided an interesting counterpoint in his review of 46 patients with XY cloacal exstrophy, penile agenesis, and penile ablation who were raised as female. Although he agreed that these patients are at greater risk of reassigning themselves to the male gender, his interpretation of the data was that core gender identity is not fully developed as a result of prenatal exposure to androgens. He admitted that the issue remains unsettled but encouraged clinicians to consider potential sexual functioning, fertility, and overall quality of life when deciding on management strategies.

Schober and coworkers[157] studied five XY cloacal exstrophy patients and four XX patients, all raised as female. They administered a questionnaire designed to address social adjustment and relationships using domains defined by the World Health Organization, including assessment of psychological well-being, level of independence or perception of disability, medical care, physical condition, and gender role. Although they found some discordance in overall satisfaction of body image in the XY patients raised female, the scores across all other domains were strikingly similar.

Given the controversy surrounding the issue of gender assignment, it is not possible at this time to define specific management guidelines. One firm area of consensus is that these decisions must be made in conjunction with parental counseling with full disclosure of all relevant information.

Surgical Reconstruction

Complete surgical reconstruction may be considered in an infant who is medically stable. This includes closure of the omphalocele, closure of the bladder and urethra, bony pelvis closure, and repair of the external genitalia. Cloacal exstrophy patients should undergo carefully planned and individualized reconstruction procedures.[158,159] In infants with spinal dysraphism and myelocystocele, neurosurgical consultation should be obtained, and closure should be undertaken as soon as the infant is medically stable. After closure of the myelocystocele, long-term follow-up is mandatory to evaluate for subtle changes in neurologic examination findings that could herald cord tethering.

Once the infant has recovered from closure of the myelocystocele, reconstruction should focus on the management of the gastrointestinal tract. Omphalocele closures are combined with gastrointestinal diversion or reconstruction. Formerly, initial attempts focused on ileostomy with resection of the hindgut remnant. With the recognition of the metabolic changes in patients with ileostomy, the hindgut remnant was used to provide an additional length of bowel for fluid absorption.[153] Enlargement of the hindgut remnant and increased water absorption have been noted in children who have had the segment incorporated into construction of a fecal colostomy. The hindgut segment may be anastomosed in an isoperistaltic or retroperistaltic fashion to decrease motility and generate formed stool. Children who have adequate colon, less severe spinal abnormalities, good sphincter functionality, and the ability to produce formed stools may have the capability for later continence and may be treated with a pull-through procedure. If the hindgut remnant is not used for bowel reconstruction, it should be left as a mucous fistula to be used for later bladder augmentation or vaginal reconstruction.[153] If gastrointestinal reconstruction is combined with bladder closure, approximation of the pubis with osteotomy is beneficial, and reconstruction of the pelvic ring increases the potential for successful bladder and abdominal wall closure.

Role of Osteotomy

Osteotomy is indicated in all children with cloacal exstrophy at the time of bladder closure because of the wide pubic diastasis that is invariably present. Osteotomy allows the pelvic ring, bladder, and abdominal wall to be closed without undue tension on the closure. Reduction in the incidence of dehiscence and postoperative ventral hernias has been noted in patients treated with osteotomy. In a large series reported by Ben-Chaim and associates,[160] significant complications occurred in 89% of patients who underwent closure of cloacal exstrophy without osteotomy, whereas these occurred in only 17% of patients who underwent osteotomy at the time of initial closure. Patients in the two groups were similar in terms of the size of the omphalocele, the presence of myelomeningocele, and the time of primary closure. However, osteotomy had no effect on the eventual continence of cloacal exstrophy patients.

Currently, combined anterior innominate and vertical iliac osteotomies are routinely used at our institution.[160] This approach does not require the patient to be repositioned on the operating table before bladder and abdominal wall closure procedures are commenced. The use of a posterior approach and any complications from this procedure related to the spinal and lower back closure are obviated. In a 1999 series of five patients with extreme pubic diastasis (>10 cm), Silver and coworkers[161] described an initial pelvic osteotomy and gradual closure of the pelvic fixator for 1 to 2 weeks, followed by abdominal wall and bladder closure. Closure was successful in all patients without technical problems or surgical complications. This technique of staged pelvic closure also proved reliable in a large series[162] for secondary repair of cloacal exstrophy when one-stage pelvic closure was unfeasible.

Bladder and Phallic Reconstruction

Urinary tract reconstruction may be performed at the time of omphalocele closure. The medial edges of the bladder halves are initially closed to generate a bladder exstrophy that can be closed and placed into the pelvis if complete repair is feasible in the newborn period. Inguinal hernias are repaired if identified. In the genetic female and genotypic male patient undergoing gender reassignment, reconstruction should be performed to improve the appearance of the genitalia.

Reconstruction of the genitalia in the immediate postnatal period is performed to make the infant appear more congruent with the assigned gender. Understanding of the psychology of children who have had gender reassignment has fueled interest in male gender assignment if adequate unilateral or bilateral corporal tissue is present.[163] Studies indicate a normal histologic appearance in the testes of male patients who have had gender reassignment, despite the presence of cryptorchidism.[163] Results of phallic reconstruction in male patients with minimal or no penile tissue in the past have been disappointing.[153,164] Techniques for creation of a pseudophallus from remote tissue transfer, such as a forearm flap, have been described, but their effectiveness in this population is still in question.[165] Conclusions from these series are a main consideration in the argument supporting assignment of the female gender to these patients. For male-to-female reassignment and in the genetic female, initial reconstruction should bring the phallic halves together at the midline as a clitoris.

However, in situations where there is adequate corporal tissue, epispadias repair can be performed at the time of initial closure, depending on the overall clinical picture.[153,158] Vaginal reconstruction should be performed early in the genetic female. In genetic male patients who require creation of a neovagina, delayed reconstruction is appropriate. Reconstruction has been performed with the use of the preserved hindgut segment, small bowel, stomach, or expanded perineal skin. Long-term dilation of the neovagina may be necessary.

Techniques to Create Urinary Continence

Urinary continence is possible in most children but usually requires bladder augmentation and the use of intermittent catheterization. Multiple series by Gearhart and Jeffs,[148] Mitchell and coworkers,[166] and Lund and Hendren[167] showed the applicability of modern reconstructive techniques for lower tract reconstruction to help these patients achieve urinary continence. Enhancement of the bladder capacity may be performed using the hindgut segment, ileum, or stomach only after consideration of gastrointestinal tract management. Continence appears to be more difficult to achieve in genetic male patients undergoing gender reassignment, and continent stomas may be most applicable in this group of patients.[153] In genetic females, successful continence had been achieved after Young-Dees-Leadbetter bladder neck reconstruction, but the vast majority required intermittent catheterization.[138] Mitchell and coworkers reported similar findings in their 1990 series.[166] Husmann and associates[168] reported their success rate of Young-Dees-Leadbetter repair in cloacal exstrophy and found that it was closely related to the severity of coexisting neurologic abnormalities.

Urinary continence can be achieved in these patients through a variety of individualized approaches.[148,166] An orthotopic urethra can be constructed from local tissue, vagina, ileum, stomach, or ureter. A catheterizable stoma can be constructed from ileum if enough bowel is present and fluid loss is not a problem. The bladder may require augmentation, and the mechanism by which this is done depends on gastrointestinal considerations. Surgery to produce a continent reservoir should be delayed until a method of evacuation can be taught and the child is mature enough to participate in self-care. The choice between a catheterizable urethra and an abdominal stoma depends on the adequacy of the urethra and bladder outlet, the interest and dexterity of the child, and the orthopedic status regarding the spine, hip joints, braces, and ambulation. An innovative approach is required to find a suitable solution for each individual patient with respect to bladder size and function, mental and neurologic status, and orthopedic status.

Long-Term Neurologic Concerns

Spinal cord untethering should be performed during the first year of life but may also be required years after closure of the myelocystocele. In a series reported by McLaughlin and colleagues in 1995,[169] changes in urinary function may be the initial evidence of tethering of the cord. Early evaluation with MRI allows rapid treatment and the prevention of further loss of function. In the previously described series of patients with long-term follow-up, the lumbosacral spinal cord was fully evaluated with myelography, CT, MRI, or some combination of these modalities in 12 patients. Spinal exploration and repair of cord tethering was done in 11 patients, 2 of whom subsequently underwent reoperation for retethering of the cord. The authors reported a 100% incidence of spinal cord or vertebral anomalies in their patients, which is higher than formerly reported in the urologic literature. MRI of the spinal cord is mandatory as part of the initial evaluation of all newborns with cloacal exstrophy, as is lifelong attention to the risk of spinal cord tethering.

Gastrointestinal Function

The growth and development of children with cloacal exstrophy strongly depends on a properly functioning gastrointestinal system.[167] Recently, a greater emphasis has been placed on preserving as much bowel as possible, in an effort to reduce metabolic dysfunction and to provide the best possible options for bowel management. Soffer and colleagues[170] recommended that initial management of the newborn should include omphalocele repair, bladder closure, and colostomy using all available colon, including the hindgut remnant. They discouraged the use of the hindgut for any genitourinary reconstruction at that time. After a year or more of observation, the decision to perform a pull-through procedure or definitive colostomy can be made based on availability of colon, neurologic status, and ability to produce formed stools. Avoidance of stomas and external appliances should be a priority if at all possible. This is a matter of convenience but also a means to avoid life-threatening complications that are seen, for example, in patients undergoing terminal ileostomy.[171] It should be noted that normal fecal continence is not the rule in these patients, even in those undergoing pull-through procedures. Therefore, a frank discussion with parents describing the ultimate need for dietary guidelines, motility agents, and enemas should be part of early management. All reconstructive strategies should be developed in consultation with the pediatric surgeons responsible for management of the gastrointestinal system, and involvement of a pediatric gastroenterologist who is interested in the complex care of these patients is mandatory.

Long-Term Psychological Issues

The psychosexual aspect of development, as described in the section on gender assignment, has been the major focus of research into the psychological well-being of these patients as they develop from children into adults. Data suggesting that almost all genetic males assigned to the female gender display male behavioral tendencies,[155] and approximately half ultimately declare themselves male, have produced an extreme reluctance and even abandonment[172] of this practice in modern management.

In the broader context of overall psychological development, available data are scarce and often conflicting. A small study by Baker-Towell and Towell[173] compared cloacal exstrophy patients with genital ambiguity to those without and found no significant difference with regard to perceived social competence, behavior, or problem scores. Their optimistic results did not prove, but certainly did suggest, that these children can be happy and well adjusted and can do relatively well.

Summary

The management of cloacal exstrophy has evolved from merely providing survival to providing improved quality of life for these children. Reconstruction using complete closure if the neonate's condition allows or the modern staged approach seems to be applicable in most patients. Neurologic and gastrointestinal management takes precedence over urologic and genital reconstruction. Improvements in diagnosis and surgical management have served to reduce life-threatening complications and progression of the neurologic deficit. Urinary continence is now possible in most children. Further advances in reconstructive surgery may someday enable congruent rearing for all male patients with cloacal exstrophy.

DEDICATION

The authors would like to dedicate this chapter to the memory of Robert Jeffs, MD, FCRS, FAAP, the first Pediatric Urology Professor at the Johns Hopkins Hospital.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 31

BLADDER DIVERTICULA, URACHAL ANOMALIES, AND OTHER UNCOMMON ANOMALIES OF THE BLADDER

Hiep T. Nguyen and Bartley G. Cilento Jr.

BLADDER DIVERTICULA

Definition and Etiology

Bladder diverticula are herniations of bladder mucosa between fibers of the detrusor muscle. Depending on the size of the muscular defect, the diverticula have either a narrow or a wide neck. Although muscle is abundant around the neck and less so in the side walls, there are only sparse detrusor muscle fibers at the dome of the diverticulum.[1] In children, the most common location for bladder diverticula is lateral and cephalad to the ureteral orifice.[2] However, in association with outlet obstruction or prune-belly syndrome, they can also occur at the dome of the bladder. Bladder diverticula are uncommon but not rare. In their pediatric genitourinary database of 5084 children, Blane and colleagues[3] found a 1.7% incidence of bladder diverticulum.

Bladder diverticula may be acquired or congenital. Acquired diverticula are usually multiple and associated with bladder trabeculation. They are the result of bladder outlet obstruction or infection or have iatrogenic causes. Bladder neck or urethral obstruction from posterior urethral valves (PUV), anterior urethral diverticulum, urethral stricture, neuropathic bladder dysfunction, or external sphincter dyssynergia increases bladder voiding pressures, forcing the bladder mucosa through the gap in the muscle of the bladder wall. These diverticula usually resolve after correction of the outlet obstruction. In children with PUV, acquired bladder diverticula can serve as a pressure pop-off mechanism to protect kidney[4,5] and bladder function.[6] Some have speculated that acquired diverticula may also develop after severe urinary infection[7]; the inflammation weakens the bladder muscle and leads to diverticula formation in the absence of outlet obstruction. Rarely, bladder diverticula are acquired iatrogenically, such as after antireflux surgery in which defects in the bladder muscular wall were not appropriately reapproximated.[8]

In the past, it was thought that all diverticula are acquired. However, it is now well recognized that the majority of bladder diverticula in children are congenital.[7,9] Congenital bladder diverticula most often are solitary, occur in a smooth wall bladder, and are more common in males. They are usually located in the lateral cornu of the trigone and the ureteral hiatus and can impinge on, engulf, or be separate from ureteral orifices (Fig. 31-1). The cause is believed to be an inherent weakness in the detrusor musculature, in particular deficiencies of the Waldeyer fascial sheath.[10] Congenital bladder diverticula have also been associated with Menkes syndrome, a neurodegenerative and connective tissue disorder with characteristic increases in tissue copper and metallothionein content[11-13]; Ehlers-Danlos syndrome, a collagen biogenesis disorder[14-17]; cutis laxa, a syndrome of decreased or absent elastic tissue (Fig. 31-2); Williams' syndrome, a disorder characterized by growth and mental retardation, facial anomalies, and aortic stenosis[3]; and prune-belly syndrome.

Presentation

Although in some children bladder diverticula have no functional consequences, in others they produce bladder outlet obstruction, vesicoureteral reflux (VUR), or ureteral obstruction or predispose to urinary tract infections. Bladder diverticula may enlarge to the extent that they compress the bladder neck or proximal urethra (Fig. 31-3).[18,19] A vicious cycle may develop in which increased outlet resistance promotes further filling of the diverticulum, resulting in increasing enlargement of the diverticulum and, consequently, increasing obstruction.[18,20] The bladder diverticula may become so large that they herniate through the femoral or inguinal canal.[21] Alternatively, bladder diverticula, especially those near the ureteral orifice, may incorporate the ureteral tunnel, resulting in VUR (Fig. 31-4).[22] However, it remains unclear whether paraureteral diverticula cause reflux or are merely associated with it.

In the literature, the incidence of VUR in association with paraureteral diverticula ranges from 5% to 100%, whereas the incidence of primary reflux associated with paraureteral diverticula ranges from 8% to 13%.[3,7,23] In the past, the presence of reflux with a paraureteral diverticulum dictated excision of the diverticulum and ureteral reimplantation. Subsequently, it was observed that reflux in association with a paraureteral diverticulum may regress spontaneously. Amar[22] noted that, in girls, especially those with small diverticula, the associated reflux resolves spontaneously as the bladder matures; in boys, the diverticula tended to be larger, and the associated reflux was less likely to disappear. More recently, Afshar and colleauges[24] retrospectively evaluated the resolution of VUR in children with and without congenital paraureteral diverticula. They observed that Kaplan-Meier analysis and the log rank test did not demonstrate any difference in resolution rate between the two groups; multivariate analysis demonstrated grade as the only variable affecting the outcome. Currently, it is generally accepted that the extent to which bladder diverticula cause VUR depends on the dynamic interaction between the ureteral orifice and the diverticulum. The ureteral orifice that becomes incorporated into the diverticulum on filling is likely to reflux, owing to the displacement of the ureteral orifice from the trigone and the shortening of its submucosal tunnel.

Bladder diverticula may also cause ureteral obstruction.[25-27] In a large study of children with bladder diverticula, Barrett and associates[7] noted that approximately 5% of the patients had radiologic evidence of ureteral obstruction. In association with ureteral obstruction, bladder diverticula may result in ipsilateral renal dysplasia and may also obstruct the contralateral ureteral orifice. It is likely that the obstruction is caused by direct ureteral compression by the diverticulum; inflammation or infection leading to peridiverticular and ureteral fibrosis; or intrinsic hypomuscularity of the distal ureters and ureterovesical junction resulting in a functional obstruction of the ureterovesical junction.[27]

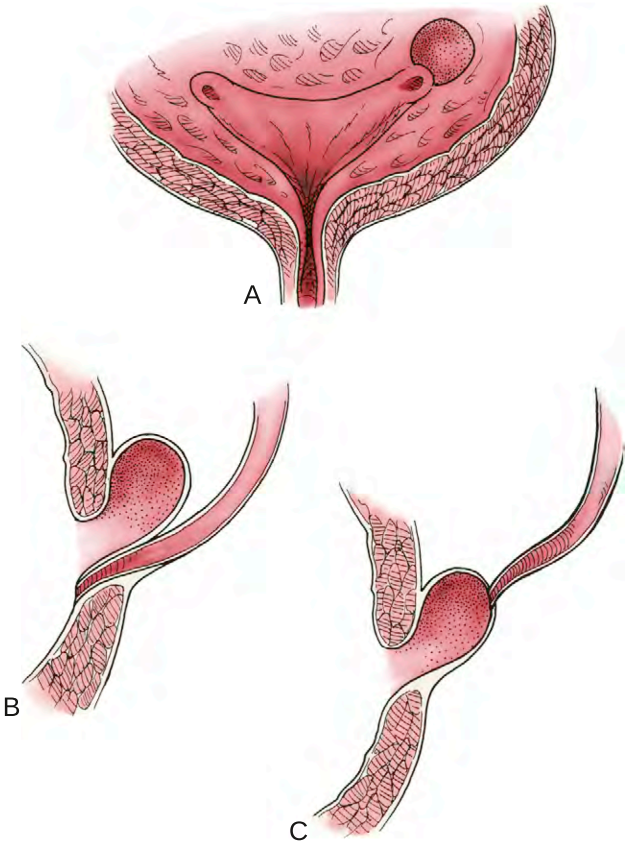

Figure 31-1 **A,** Common location for congenital bladder diverticulum. The ureters may insert near **(B)** or into **(C)** the diverticulum.

In association with bladder outlet obstruction, VUR, or ureteral obstruction, bladder diverticula may predispose to urinary tract infections. However, urinary infection can occur in children independent of obstruction or reflux. Because of a lack of musculature, large bladder diverticula do not empty on voiding, allowing stasis of urine (Fig. 31-5).[28-30] Furthermore, some children with bladder diverticula have an abnormal voiding pattern on urodynamic evaluation, including detrusor-sphincter dyssynergia, hyperreflexia, or hypotonia.[31] It remains to be determined whether bladder diverticula cause these abnormal urodynamic findings or whether such abnormalities in bladder function lead to diverticular changes. Nevertheless, these findings, in addition to urinary stasis, may predispose children with bladder diverticula to recurrent urinary tract infection. Recent small reports[32] in the literature have suggested that surgical excision of primary bladder diverticula can eliminate infections and is associated with improvement of voiding dysfunction.

Other, albeit rare, presentations of bladder diverticula have also been reported. Spontaneous perforation of a congenital bladder diverticulum may occur, resulting in abdominal pain and sepsis.[33] Although this is an uncommon cause for these symptoms, it must be considered if the etiology is not clear. Delay in diagnosis of a bladder rupture can result in morbid outcomes. Tumors may also develop in the bladder diverticula. These tumors could be urothelial in origin[34] or they could be intradiverticular sarcomas or carcinosarcomas.[35] Patients with diverticular tumors often present with gross or microscopic hematuria. The tumors tend to be more aggressive than their bladder counterparts, with a high incidence of intra-abdominal recurrences. Treatment with surgery, or chemotherapy, or both (depending on the type, grade, and stage of the tumor) is often required.

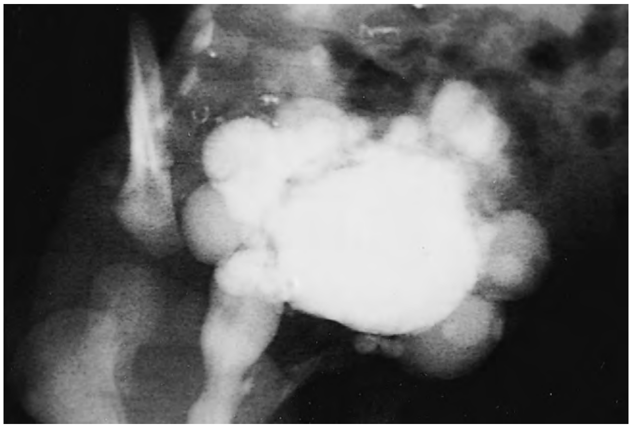

Figure 31-2 Voiding cystourethrogram demonstrates multiple bladder diverticula in a patient with cutis laxa.

Radiographic Evaluation

Bladder diverticula may be diagnosed by various radiologic methods. Because of their dynamic nature, they can be elusive on uroradiologic studies. The voiding cystourethrogram is the best modality for identifying bladder diverticula.[36] Diverticula can be detected by bladder ultrasonography, especially if it is performed with an empty and then a full bladder. Intravenous pyelograms are not sensitive in detecting bladder diverticula because they are easily overshadowed by the bladder's filling with contrast material.

Management

The management of bladder diverticula depends on the symptoms, such as infection, obstruction, or reflux. In their absence, intervention is often not necessary. However, surgical intervention may be required if there is recurrent infection, bladder outlet obstruction, persistent VUR, or functionally significant ureteral obstruction.

In the presence of bladder outlet obstruction, diverticulectomy is often necessary to relieve the obstruction of the bladder neck or proximal urethra, using open surgical, endoscopic,[37] or laparoscopic methods.[38]

For patients who have persistent reflux, diverticulectomy with ureteral reimplantation is recommended. Traditionally, this is performed intravesically, with careful attention to reinforcing the hiatus to prevent postoperative diverticula formation. However, extravesical detrusorrhaphy for the refluxing ureters associated with paraureteral diverticula can be performed with minimal postoperative morbidity and as effectively as the intravesical method.[39]

In the presence of ureteral obstruction, management depends on upper tract function of the affected renal unit, requiring either diverticulectomy with reimplantation or nephrectomy.

ANOMALIES OF THE URACHUS

Definition and Etiology

The urachus lies between the transversalis fascia and the peritoneum, adjacent to umbilical ligaments, the remnants of the umbilical arteries. The urachus is 3 to 10 cm long and 8 to 10 mm

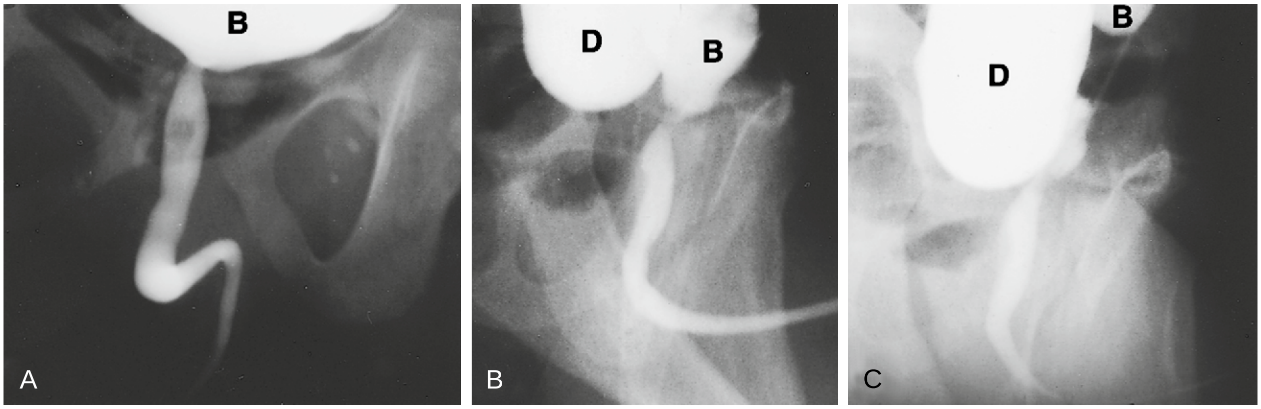

Figure 31-3 Voiding cystourethrogram demonstrates progressive filling of the bladder diverticulum (D) during voiding **(A and B)** with resultant obstruction of the outlet of the bladder (B) by the large diverticulum **(C).**

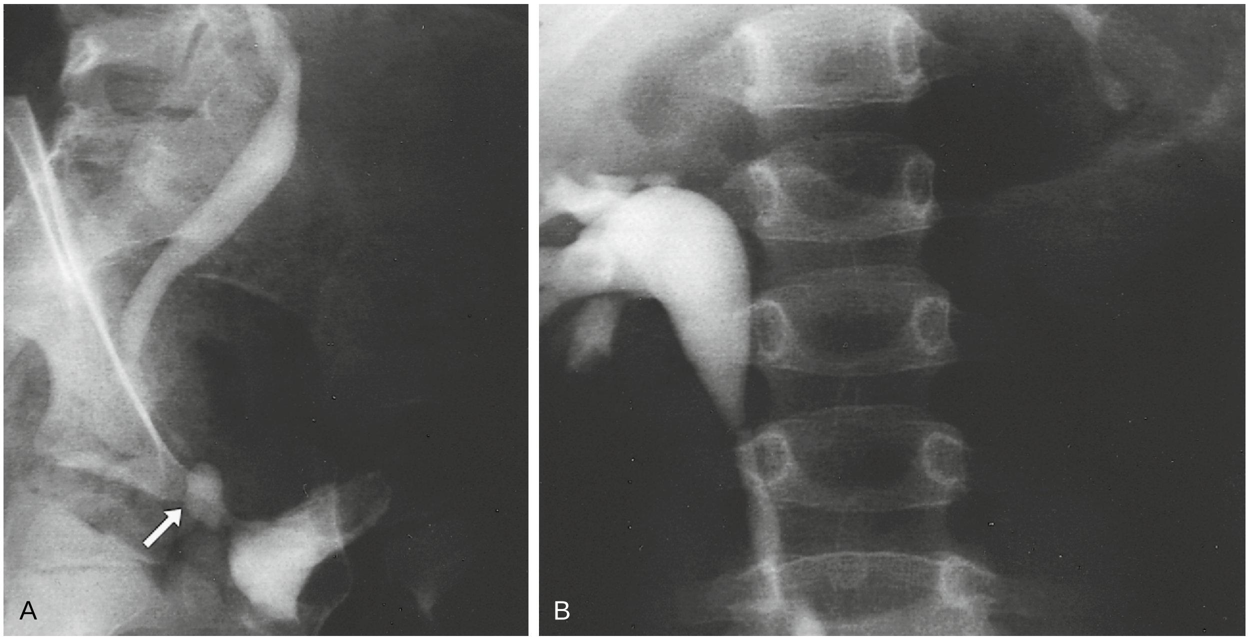

Figure 31-4 Voiding cystourethrogram demonstrates vesicoureteral reflux in a ureter that inserted into a diverticulum *(arrow)* **(A),** which allows contrast material to reflux into the upper collecting system **(B).**

in diameter. It is surrounded by the umbilicovesical fascial sheath, which extends laterally to each umbilical artery and inferiorly over the bladder dome to the hypogastric arteries posteriorly and the pelvic diaphragm anteriorly, forming a self-contained space that is capable of limiting the spread of infection or neoplasm. The urachus is composed of three histologic layers: an inner cuboidal or transition layer, a submucosal tissue layer, and an outer smooth muscle layer. The central lumen is irregular and beaded and is filled with desquamated epithelial debris.[40] In the sheep experimental model, premature closure of the urachus results in hydronephrosis,[41] suggesting that, during fetal life, the urachus provides a low-resistance outlet for drainage of the bladder while the urinary sphincter matures.

Embryologically, the majority of the urachus is derived from the bladder, and the proximal portion is formed from the allantoic duct.[42] As the bladder descends into the pelvis, it retains its attachment to the umbilicus by the urachus. As the urachus develops, it loses its attachment to the umbilicus. Based on the differential growth rates of the urachus, anterior abdominal wall, and bladder descent, four anatomic variants of urachal termination result (Fig. 31-6).[43,44] In type I, the urachus fails to atrophy, retaining its attachment to the dome of the bladder, separate from each umbilical artery. A type II variant results when the urachus fuses with one of the umbilical arteries and continues as a single fibrous cord to the umbilicus. In type III, the urachus fuses with both the umbilical arteries and continues as a single structure to the umbilicus. Finally, a type IV variant occurs when the urachus forms an atrophied tube that terminates before fusing with the umbilical arteries, ending within the fascia or blending into a plexus of fibrous tissue (the plexus of Luschka) formed by the urachus and the umbilical arteries.[42] Between the 4th and 5th month of gestation, the potential communication between the apex of the bladder and the urachal canal is segmentally obstructed by desquamated epithelium.[40]

Presentation and Radiographic Examination

Congenital anomalies of the urachus, including urachal sinus, urachal cyst, patent urachus, and vesicourachal diverticulum (Fig. 31-7), represent an arrest of the normal involutionary

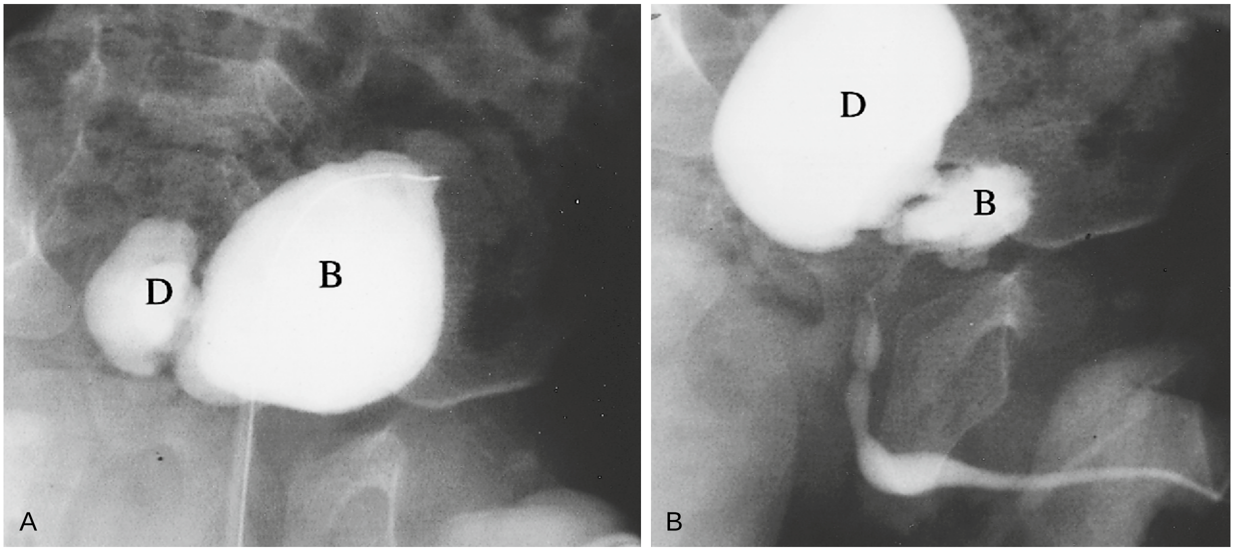

Figure 31-5 Voiding cystourethrogram demonstrates filling of the diverticulum (D) during bladder (B) filling **(A)** and during voiding **(B).** The bladder diverticulum may fill during voiding and, because of its lack of musculature, cannot empty.

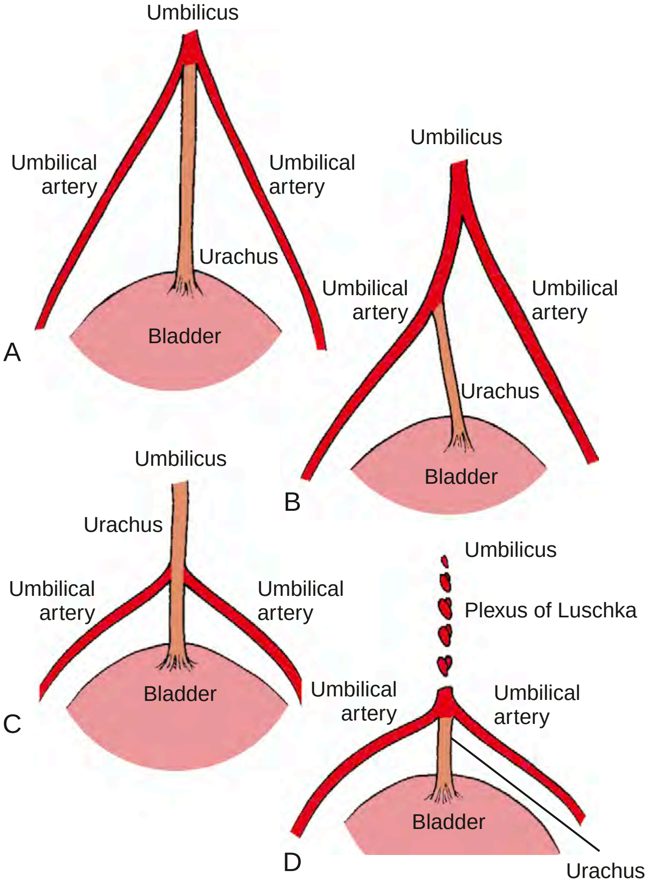

Figure 31-6 Four types of variant in urachal termination: **A,** type I: **B,** type II; **C,** type III; **D,** type IV. See text for descriptions.

process of the urachus. They rarely manifest in childhood and may not be symptomatic until adulthood. In symptomatic patients, these anomalies are seen equally in males and females. Common presenting symptoms include periumbilical discharge (42%), an umbilical mass (33%), abdominal or periumbilical pain (22%), and dysuria (2%).[45] Urachal anomalies usually occur as isolated defects and are not associated with other syndromes, with the exception of prune-belly syndrome or bladder outlet obstruction in association with a patent urachus. Of the urachal anomalies, urachal sinus and urachal cyst are more common (43% to 59% and 29% to 43%, respectively) than patent urachus and vesicourachal diverticulum (10% to 15% and 4% to 6%, respectively).[45-47] The diagnosis of urachal anomalies can often be made with a thorough physical examination and the appropriate radiographic test. In a child with periumbilical drainage, a sinogram should be obtained to evaluate for a urachal sinus or patent urachus. In a child with a periumbilical mass, ultrasonography should be performed and should be diagnostic for a urachal cyst.[45]

Urachal Sinus

A urachal sinus arises from a type I urachal termination variant when the urachus remains patent through part of its length (Fig. 31-8). An alternating sinus may be formed if a small urachal cyst becomes chronically infected and drains into the umbilicus or the bladder.[48] Children with urachal sinus may present with intermittent or persistent umbilical drainage, with periumbilical pain and tenderness, or with just a wet umbilicus and surrounding granulation tissue. Gastrointestinal symptoms may result if other umbilical remnants become involved in the inflammatory process. In the presence of a sinus at the umbilicus, a sinogram with radiopaque material is diagnostic.[45]

Treatment of urachal sinus is directed toward controlling the associated infection, after which complete excision of the sinus tract along with resection of the omphalomesenteric duct remnants should be performed.[44] At the time of resection, care should be taken to avoid damaging intraperitoneal structures that may be densely adherent to the inflammatory mass.

Urachal Cyst

A urachal cyst develops most commonly in the distal third of the urachus but can occur in the proximal third, depending on the type of urachal termination variant. In a type II or III variant in which the umbilical end of the urachus is obliterated, a cyst filled with desquamated epithelium can develop

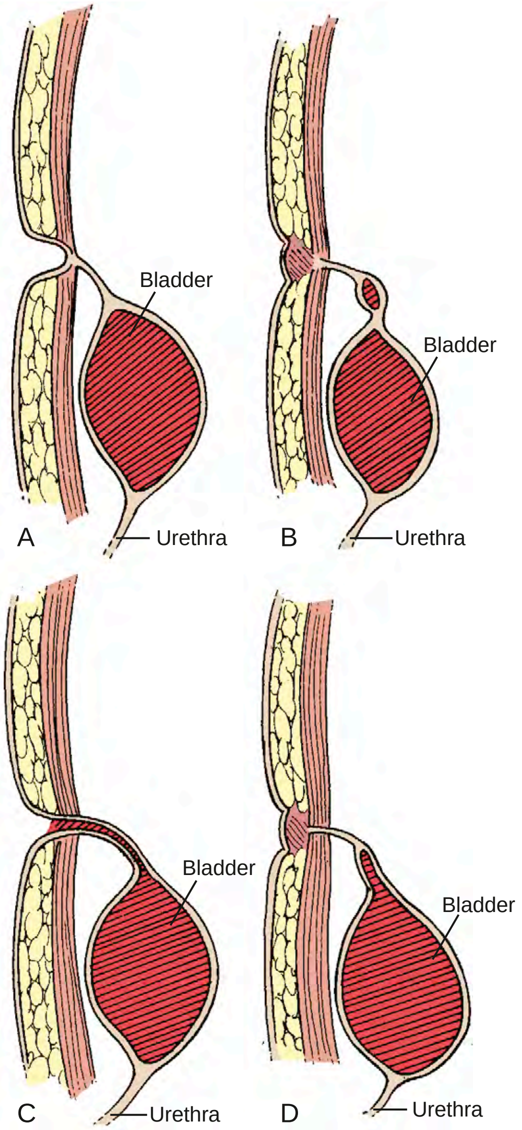

Figure 31-7 Four types of urachal anomalies: **A,** urachal sinus; **B,** urachal cyst; **C,** patent urachus; **D,** vesicourachal diverticulum.

in the bladder end (distal third of the urachus). Alternatively, in a type IV variant, degeneration of one of the plexuses of Luschka results in a cyst in the proximal third of the urachus.[48] In autopsy series, the incidence of urachal cyst is 1 in 5000.[49] Urachal cysts rarely manifest in the newborn period but may become symptomatic during late childhood or in early adult life. The presenting symptoms of children with urachal cyst include an asymptomatic suprapubic mass, fever with suprapubic pain, or irritative voiding symptoms with a palpable suprapubic mass. Not uncommonly, the urachal cyst may become infected, with *Staphylococcus aureus* the most common bacterium cultured.[50] Because of the anatomy and location of the urachal cyst, infection is usually limited to the space of Retzius, but occasionally, an infected cyst ruptures into the peritoneum with resultant bowel fistula formation.[51] The diagnosis of urachal cyst is most often made by ultrasonography, delineating the location of the cyst relative to the bladder and peritoneum and the limit of extension (Fig. 31-9).[45] Computed tomography may be occasionally useful in further defining the extent of the cyst and the involvement of adjacent

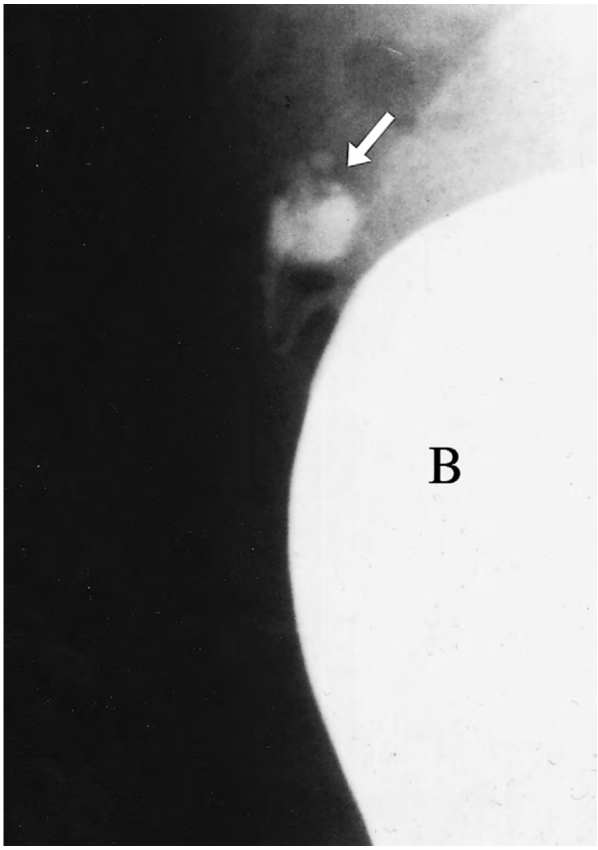

Figure 31-8 Contrast material fills in the bladder (B) and in the urachal sinus *(arrow)*.

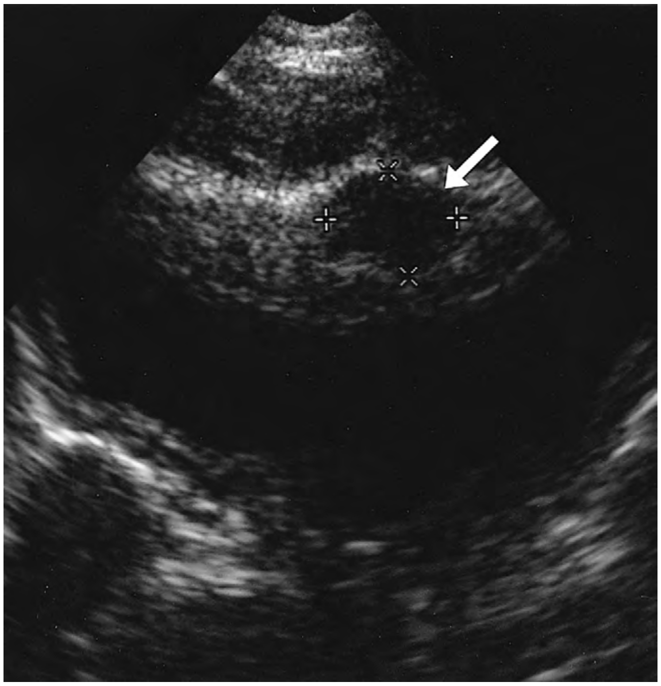

Figure 31-9 Ultrasound study shows a urachal cyst *(arrow)* located anterior to the bladder.

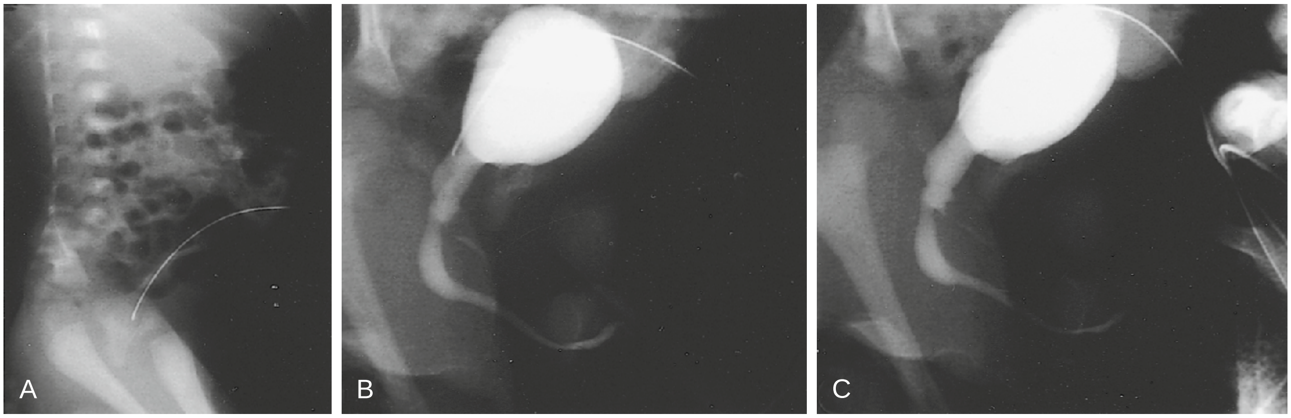

Figure 31-10 Voiding cystourethrogram demonstrates a catheter in the patent urachus **(A),** with subsequent filling of the bladder with contrast material through the patent urachus **(B)** and voiding through the urethra **(C).**

structures such as bowel. Intravenous pyelography, voiding cystourethrography, or cystoscopy can be done to evaluate the degree of involvement of the bladder wall.[48]

Treatment for urachal cyst depends on the presenting symptoms. For children in whom the urachal cyst presents as an asymptomatic mass, observation may be appropriate for small cysts. With an infected urachal cyst, the initial treatment may include incision and drainage, marsupialization, or percutaneous catheter drainage. Definitive treatment with surgical excision should be performed after the inflammation subsides. This staged approach to treating infected urachal cysts helps to limit the amount of bladder wall resected and reduces the risk of injury to adjacent intraperitoneal structures.

Patent Urachus

A patent urachus—a communication between the umbilicus and the bladder—results from the failure of a type I urachal termination variant to obliterate by desquamation of its epithelial mucosa. In autopsy series, the incidence of a patent urachus is 1 in 761.[49] A patent urachus may be seen in patients with prune-belly syndrome but is uncommon in those with PUV.[52] Patent urachus may manifest as an incidental finding on newborn ultrasonography; as a wet umbilicus with surrounding granulation tissue; as intermittent or continuous urinary drainage that is accentuated in the prone position or with crying, straining, or voiding; or as a periumbilical swelling or mass secondary to an associated umbilical hernia or engorgement of the urachal vasculature.[48] The diagnosis of a patent urachus in patients with these symptoms should be differentiated from that of omphalitis, granulation of a healing umbilical stump, patent vitelline or omphalomesenteric duct, infected umbilical vessel, and external urachal sinus. Analysis of periumbilical fluid for creatinine or urea is useful in differentiating a patent urachus from these other conditions, and a fistulogram with radiopaque material is often diagnostic.[45] A voiding cystourethrogram should be obtained to identify the fistula tract (Fig. 31-10) and, more importantly, to rule out the concomitant presence of bladder outlet obstruction or VUR.

In the management of a patent urachus, observation may be indicated for young infants without symptoms, because the involution of the urachus is not complete at birth, and spontaneous closure can occur during the first months of life.[53] In patients who have a patent urachus in association with bladder outlet obstruction, treatment of only the bladder outlet obstruction is often adequate, because spontaneous closure of the patent urachus usually occurs after adequate relief of bladder outlet obstruction. However, if drainage continues for several months, excision of the urachal tract and cuff of bladder through an extraperitoneal approach may be required.[54]

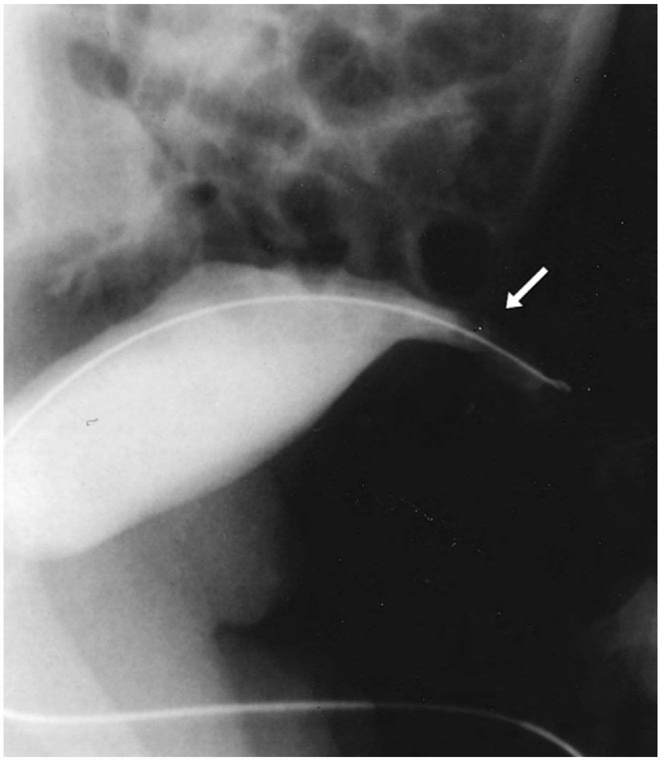

Figure 31-11 Voiding cystourethrogram demonstrates a catheter placed into a vesicourachal diverticulum *(arrow).*

Vesicourachal Diverticulum

Vesicourachal diverticulum develops when the communication between the bladder and the urachus fails to obliterate in a type II or III urachal termination variant, resulting in a fusiform outpouching at the apex of the bladder (Fig. 31-11). The diverticulum is often nonobstructive, drains well, and therefore does not predispose to stagnation of urine or infection.[48] It may be found in association with prune-belly syndrome and other bladder outlet obstructive disorders. However, vesicourachal diverticulum can also occur in the absence of functional or anatomic obstruction.

The diverticulum does not usually require treatment. On the rare occasions when it is large, empties poorly because of a narrowed neck, or contracts paradoxically, excision of the vesicourachal diverticulum may be required.

Management

Although most of these urachal anomalies are treated surgically, some patients with these anomalies are observed. Urachal carcinoma may develop within these anomalies, but it is rare in children (0.01%[55]) and accounts for fewer than 0.34% of all bladder cancers.[56,57] The most common histologic type is adenocarcinoma, but other types have been reported, including transitional cell carcinoma,[57] neuroblastoma,[55] rhabdomyosarcoma,[58] teratoma,[59] yolk sac carcinoma,[60] and inflammatory myofibroblastic tumors.[61] Patients with urachal carcinoma most often present with hematuria and a palpable mass. The most common finding on radiologic evaluation is a filling defect within the bladder, with stippled calcifications. Patients with adenocarcinoma of the urachus have improved overall and disease-specific mortality risks compared to those with adenocarcinoma of the bladder.[62] However, the prognosis of patients with urachal adenocarcinoma often remains poor because of late presentation with local invasion. Close radiologic evaluation is therefore warranted in children with urachal anomalies.

OTHER UNCOMMON ANOMALIES OF THE BLADDER

Bladder Ears

Bladder ears are lateral protrusions of the bladder wall into the internal inguinal ring. They are seen frequently on intravenous pyelography or voiding cystourethrography but usually recede when the bladder is filled to capacity (Fig. 31-12).[48] They are caused by the close proximity of the infant bladder to the internal rings and are rarely seen in adults. Treatment is usually not necessary, because most resolve spontaneously with the growth of the bladder. However, on occasion, bladder ears may herniate into the internal ring and be accidentally resected during herniorrhaphy.[63,64]

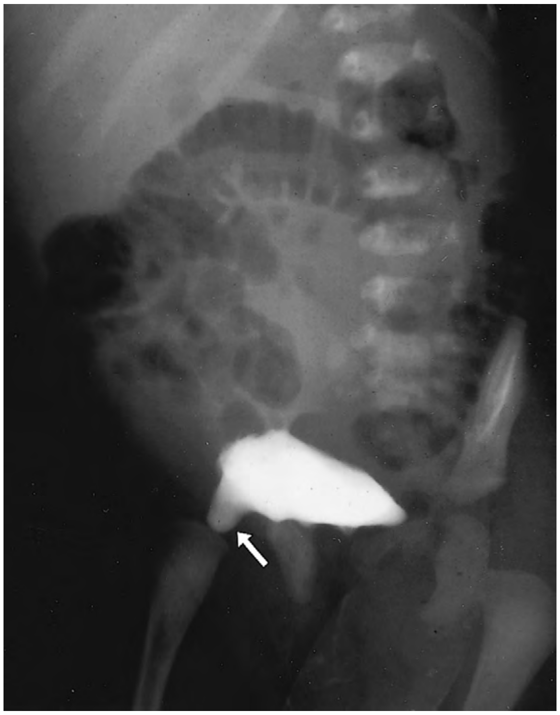

Figure 31-12 Voiding cystourethrogram demonstrates a bladder ear *(arrow)*.

Bladder Agenesis

Bladder agenesis is a rare anomaly in viable newborns[65,66]; most with this anomaly do not survive. Fewer than 20 live births of infants with bladder agenesis have been reported in the literature, with the majority being girls.[67-69] Although most of these patients are diagnosed during infancy, some patients with bladder agenesis are not diagnosed until a later age.[67] In the absence of the bladder and trigone, the ureteral orifices follow the terminations of the mesonephric ducts and enter into the urethra, the vestibule, or Gartner duct in the female or the prostatic urethra in the male; or they may enter the rectum or the patent urachus.[69-72] The ureters may remain separate or form a common channel. They are often hydronephrotic with or without associated renal dysplasia. Bladder agenesis is most often associated with neurologic, orthopedic,[73] or other urogenital anomalies such as solitary kidney, renal agenesis, renal dysplasia, or an absence of the prostate, vagina, seminal vesicles, or penis.[68,74,75] Hindgut abnormalities can occur,[76] but the hindgut is usually normal. Palmer and Russi[70] postulated that bladder agenesis results from failure of the lower portions of the mesonephric ducts to develop into the mesodermal portion of the bladder. More specifically, Krull and associates[69] suggested that, in bladder agenesis, there is a failure of incorporation of the mesonephric ducts and ureters into the trigone, which prevents urine from accumulating in the developing bladder. Consequently, the bladder fails to develop due to a lack of distention with urine. In patients with bladder agenesis, initial treatment with urinary diversion is necessary, with complex urinary construction undertaken at a later age when appropriate.

Bladder Hypoplasia and Megacystis

In congenital hypoplasia of the bladder and megacystis, it is believed that inadequate or excess filling of urine results in underdevelopment or overdevelopment of the fetal bladder. A hypoplastic bladder with little capacity develops in those disorders in which an inadequate amount of urine is stored in the fetal bladder (severe epispadias with incontinence, urogenital sinus abnormalities in females, bilateral renal agenesis, severe renal dysplasia) or the bladder is bypassed altogether (bilateral ureteral ectopia with distal urethral or vaginal orifices in the female).[48] The congenital hypoplastic bladder can improve with refunctionalization but more commonly requires augmentation.

In contrast, primary congenital megacystis is associated with massively refluxing megaureters and an excess amount of stored urine during bladder development (Fig. 31-13). Congenital megacystis was previously attributed to congenital bladder neck obstruction.[77,78] However, it was subsequently recognized that megacystis most likely results from the constant recycling of urine between massively dilated upper tracts and the bladder.[79] In patients with congenital

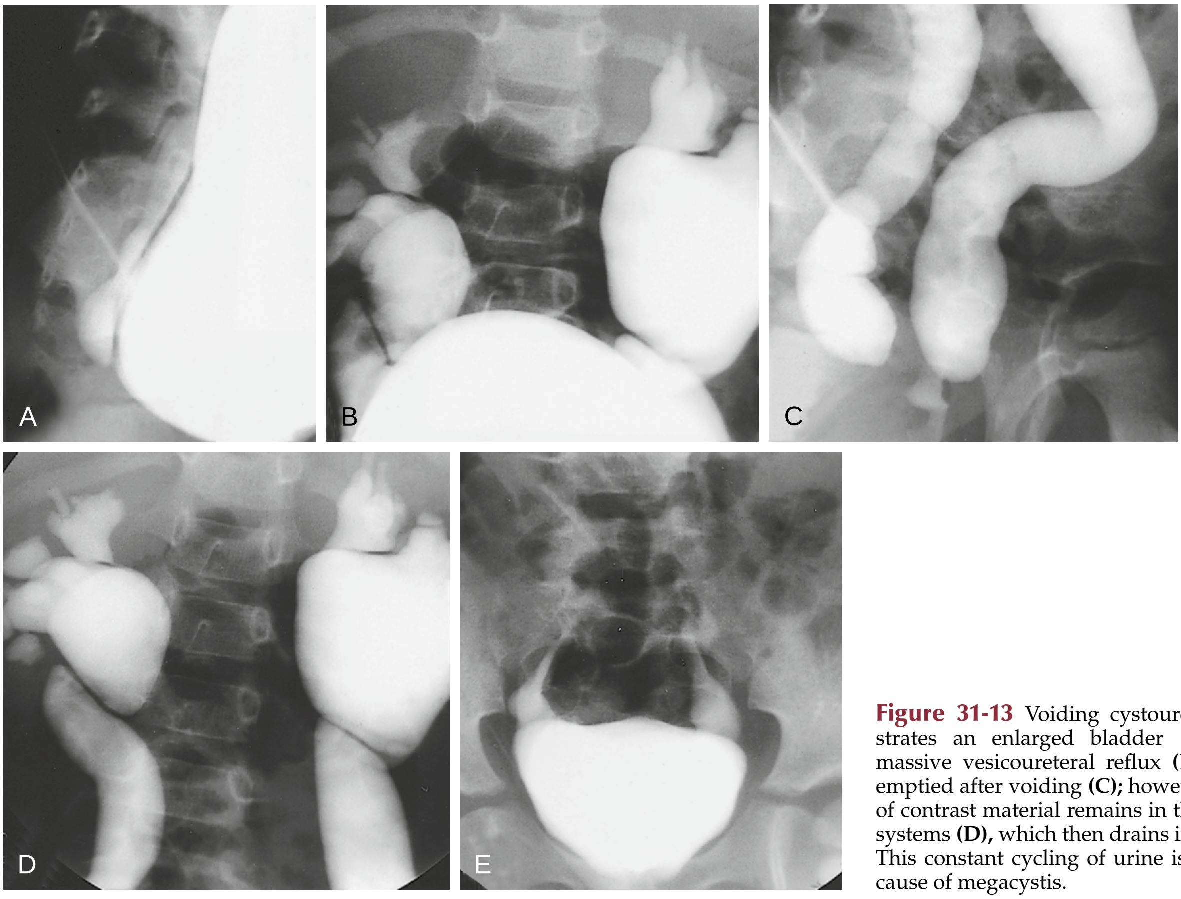

Figure 31-13 Voiding cystourethrogram demonstrates an enlarged bladder **(A)** with bilateral massive vesicoureteral reflux **(B).** The bladder is emptied after voiding **(C);** however, a large amount of contrast material remains in the upper collecting systems **(D),** which then drains into the bladder **(E).** This constant cycling of urine is thought to be the cause of megacystis.

megacystis, the trigone is wide and poorly developed, with gaping, laterally displaced ureteral orifices. These bladders are able to contract and empty normally, although much of their capacity goes into the upper urinary tracts. The diagnosis can be made prenatally, and the patients should be started on prophylactic antibiotic therapy.[80] Congenital megacystis can also be seen in association with microcolon-intestinal hypoperistalsis syndrome[81,82] or Ehlers-Danlos syndrome[83] or secondary to outlet obstruction such as that caused by PUV, urethral diverticulum, anterior sacral meningomyelocele, sacrococcygeal teratoma, pelvic neuroblastoma, or cystic duplication of the rectum. The treatment of primary congenital megacystis is primarily directed at correcting the massive VUR, and reduction cystoplasty is often not needed.[84] However, antireflux surgery in patients with congenital megacystis is often difficult to perform because of the thinness of the bladder wall. In patients with secondary forms of congenital megacystis, treatment of the obstruction is often adequate, and reduction cystoplasty is not routinely recommended.

Bladder Duplication

Bladder duplication anomalies can be classified as complete or incomplete. In complete duplication, two bladder halves are present, each with a full-thickness muscular wall and mucosa (Fig. 31-14).[85,86] Each bladder half is on one side of the midline, has an ipsilateral ureter, and drains into its complementary urethra. Fewer than 50 cases of complete bladder duplication have been reported in the literature. This duplication anomaly is more common in males. In 90% of cases, there is an associated complete duplication of the penis in the male or of the vagina

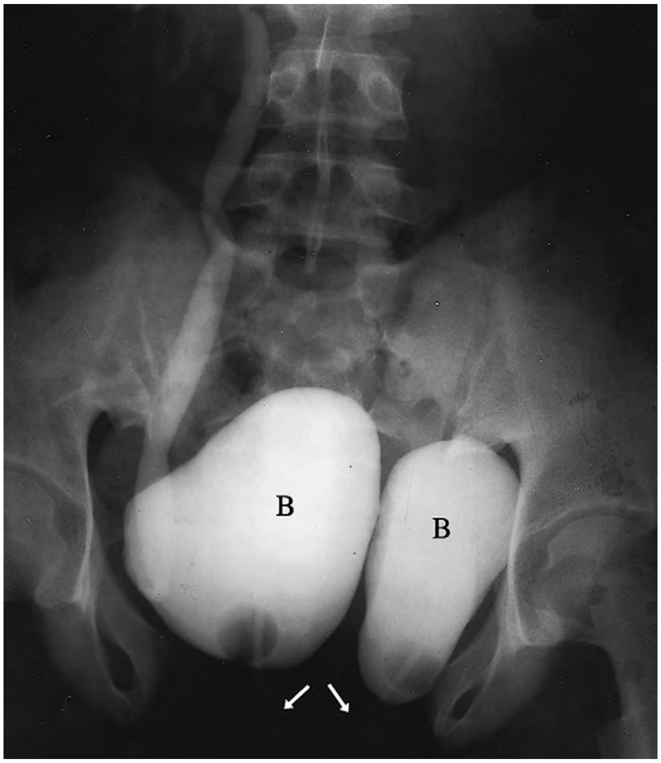

Figure 31-14 Voiding cystourethrogram demonstrates contrast material filling two separate bladders (B) through two urethras *(arrows).* There is reflux into the right collecting system. Each bladder has a separate renal unit emptying into it.

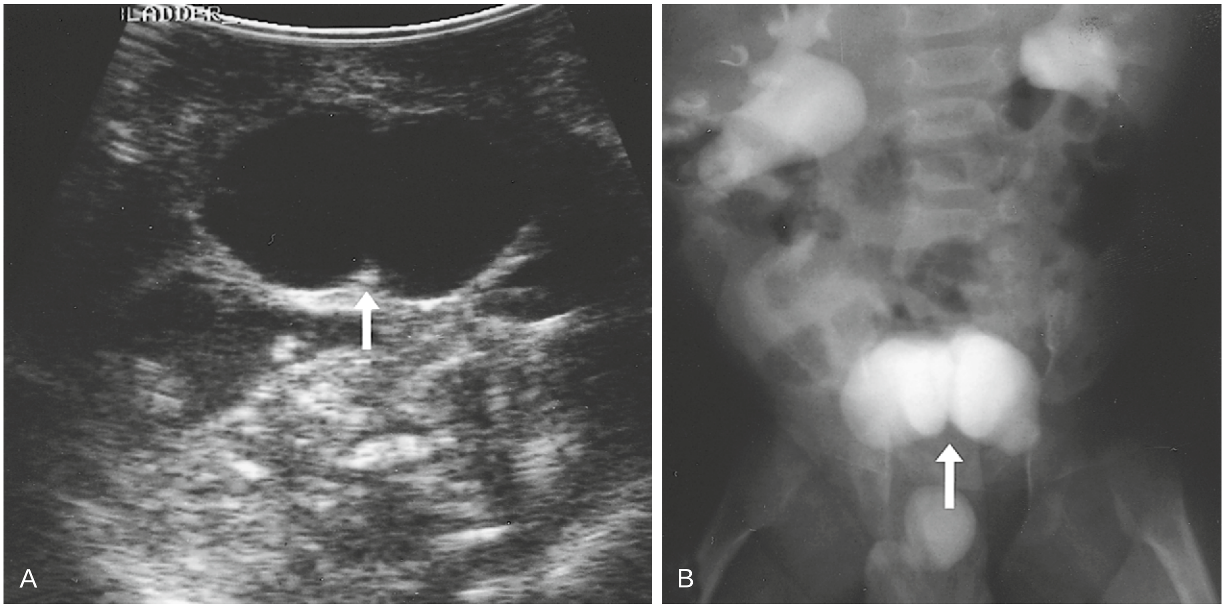

Figure 31-15 Ultrasound study **(A)** suggests the presence of bladder septation *(arrow)*, which was later confirmed on intravenous pyelography **(B).**

and uterus in the female.[87,88] In 40% to 50% of the cases, the hindgut is also duplicated.[87,89] Lumbar vertebral duplication and fistulas between the rectum, vagina, and urethra may also be present. Major reconstructive surgery may be necessary for some of these patients.

In incomplete duplication, the bladder is divided by a full-thickness wall, either sagittally or coronally.[90,91] The two bladder halves, each with an ipsilateral ureter, communicate and drain into one common urethra. Incomplete bladder duplication is less common than its complete counterpart. In contrast to complete bladder duplication anomalies, genital and anorectal anomalies are not usually associated with the incomplete form. Usually, incomplete bladder duplication does not result in serious sequelae.[92]

Compartmentalization Anomalies of the Bladder

Compartmentalization anomalies such as septated, multiloculated, or hourglass bladder are often misdiagnosed as ectopic ureteroceles, bladder or urachal diverticulum, or dilated posterior urethra secondary to PUV. In the septated bladder, the bladder body is divided, completely or incompletely, in either the frontal or sagittal plane, by a partition of mucosa alone or with muscularis and mucosa (Fig. 31-15). One ureter enters each compartment, and there is a single bladder neck and urethra. Thus, complete bladder septation is associated with dysplasia or obstruction of one unit (which in turn can obstruct the contralateral unit).[48] In contrast, both compartments in the incomplete septated bladder drain freely.

In a multiloculated bladder, the rarest of the septation anomalies, fibromuscular walls compartmentalize the bladder body into unequal chambers. The serosal surface of the multiloculated bladder appears normal. The upper tracts are usually duplicated, with each entering into a separate chamber. The renal units to the blind compartments are dysplastic or obstructed, or both.[48]

Surgical treatment of these compartmentalization anomalies should be tailored for each patient, taking into account whether the bladder segments are obstructed and the degree of renal dysplasia associated with the obstructed bladder segments.

ACKNOWLEDGMENT

We thank Dr. Robert Lebowitz for his invaluable assistance with the photographs in this chapter.

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CHAPTER 32

PRUNE-BELLY SYNDROME

Anthony A. Caldamone and John R. Woodard

Prune-belly syndrome (PBS) is a syndrome with a broad spectrum of severity. It is a constellation of anomalies. The three major aspects are abdominal musculature deficiency, bilateral intra-abdominal testes, and an anomalous urinary tract. The urinary tract is characterized by variable degrees of hydronephrosis, renal dysplasia, dilated tortuous ureters, an enlarged bladder, and a dilated prostatic urethra. Associated anomalies involving the respiratory tract, gastrointestinal tract, cardiac system, and musculoskeletal systems also occur. There is a broad spectrum of severity of the syndrome, with some children who do not survive the newborn period and others who are minimally affected. The single most important determinant of survival is usually the severity of the urinary tract anomaly, and in particular, the degree of renal dysplasia.

Osler's vivid description of the abdominal wall of an infant with the characteristic findings led to the term "prune-belly syndrome."[1] However, Frolich[2] first described the characteristic abdominal wall in 1839, and the full triad of anomalies was described by Parker[3] in 1895. Other names that have been applied to this syndrome include triad syndrome, Eagle-Barrett syndrome, and abdominal musculature syndrome.[4,5]

The incidence of PBS has been reported to be between 1 in 29,000 and 1 in 40,000 live births, similar to that of bladder exstrophy,[6] with 95% of cases occurring in males.[7] Females with PBS have the abdominal wall deficiency and urinary tract dysmorphism without any gonadal anomaly.[8,9] A higher incidence is noted among twins, blacks, and children born to younger mothers. The incidence appears to be declining in recent years, possibly due to prenatal diagnosis and a decision to terminate the pregnancy.

EMBRYOLOGY

There have been several theories as to the embryogenesis of PBS. However, there is no experimental model that can be used to test these theories, so the exact mechanism remains elusive. The four principal theories are (1) early in utero posterior urethral obstruction resulting in severe dilation of the urinary tract and possible fetal ascites and oligohydramnios[7,10-12]; (2) a primary defect in the lateral plate mesoderm, which is the precursor of the ureters, bladder, prostate, urethra, and gubernaculum[13,14]; (3) an intrinsic defect of the urinary tract leading to ureteral dilation and fetal ascites[15-19]; and (4) a yolk sac defect.[20,21] None of these theories has universal acceptance, and there is some overlap among them.

GENETICS

A genetic basis to PBS is suggested by the high male-to-female ratio, occasional occurrence in male siblings and cousins, and the increased occurrence in twins. Yet most cases are sporadic and have a normal karyotype. One in 23 children with PBS is the product of a twin pregnancy.[13] However, the majority of reported twins have been discordant for PBS, evidence against a genetic etiology. It has been suggested that the etiology in twins may be an uneven distribution of mesenchymal tissue at a critical time of primitive streak development during the third week of embryogenesis.[22] There are reported associations with Turner syndrome, monosomy 16, trisomy 13, and trisomy 18.[23,24] A variety of inheritance patterns have been proposed, including X-linked recession,[25] a two-step autosomal dominant mutation,[26] and polygenetic transmission.[27-29] A recent report by Ramasamy and colleagues[30] suggested a sex-influenced autosomal recessive mode of inheritance in familial PBS. The consensus, however, remains that an associated chromosomal abnormality is the exception rather than the rule, because most patients have a normal karyotype. More recent reports have noted an association between PBS and Beckwith-Weidemann syndrome.[31,32]

CLINICAL FEATURES OF PRUNE-BELLY SYNDROME

Extragenitourinary Abnormalities

Of all children with PBS, 75% have nonurinary tract abnormalities.[33] After the obvious abdominal wall defect, the most common abnormalities are cardiac, pulmonary, and orthopedic (Table 32-1).

Abdominal Wall Defect

The appearance of the abdominal wall gives PBS of newborns their most characteristic feature (Fig. 32-1). In some cases, the musculature of the abdominal wall is totally absent,[34] but most commonly there is uneven involvement. The medial and inferior muscles typically are most deficient.[35,36] The appearance at birth is that of wrinkled, redundant skin with an abdomen that bulges in the flanks. One may be able to discern intra-abdominal organs through the thinned abdominal wall. The most severely affected areas may have skin, subcutaneous fat, and a single fibrous layer on the peritoneum.[36,37] Randolph and coworkers conducted electromyographic imaging and demonstrated the inferior and medial segments to be most consistently affected.[38] Electron microscopy has demonstrated a nonspecific pattern of myofilament disarray, Z-line disorganization, and mitochondrial proliferation.[39-41] The fact that normal spinal anterior horn cells have been shown rules out a neuropathic etiology for the muscular deficiency.[42] The muscular deficiency is typically inconsistent and patchy.

As the child gets older, the abdomen becomes less wrinkled and takes on more of a pot-bellied appearance (Fig. 32-2). Gait usually is not affected, although it may be delayed, and the children tend to roll to their side and use their arms to sit from a supine position. The poor support of the lower chest wall results in flaring of the costal margin.[41] These children are more vulnerable to respiratory illnesses because their cough effectiveness is compromised. In spite of these abdominal wall issues, Woodard and Smith reported good wound healing with no tendency toward infections or incisional hernias.[41]

Cardiac Anomalies

Cardiac anomalies, such as patent ductus arteriosus, atrial septal defect, ventricular septal defect, and tetralogy of Fallot, occur in 10% of children with PBS.[43] Cardiac abnormalities at birth may take precedence over urologic issues.

Table 32-1 Extragenitourinary Abnormalities

Cardiac	Patent ductus arteriosus Ventricular septal defect Atrial septal defect Tetralogy of Fallot
Pulmonary	Lobar atelectasis Pulmonary hypoplasia Pneumothorax Pneumomediastinum
Gastrointestinal	Intestinal malrotation Intestinal atresias or stenosis Omphalocele Gastroschisis Hirschsprung's disease Imperforate anus Hepatobiliary anomalies
Orthopedic	Pectus excavatum, pectus carinatum Scoliosis Sacral agenesis (partial) Congenital hip subluxation or dislocation Genu valgum Talipes equinovarus Severe leg maldevelopment
Miscellaneous	Splenic torsion Adrenal cystic dysplasia

Modified from Woodard JR, Smith EA. Prune-belly syndrome. In: Walsh PC, Retik AB, Vaughan ED Jr, Wein AJ, eds. *Campbell's Urology*. 7th ed. Philadelphia: WB Saunders; 1998:1991

Pulmonary Abnormalities

Pulmonary difficulties can be observed at any age in patients with PBS. Pulmonary hypoplasia can result from severe oligohydramnios due to renal dysplasia or severe bladder outlet obstruction and may result in death of the newborn. In addition, pneumothorax and pneumomediastinum can be seen with or without pulmonary hypoplasia.[44] Significant pulmonary difficulties have been reported in 55% of PBS survivors.[33] The lack of ability to generate significant intra-abdominal pressure may contribute to pneumonia and lobar atelectasis.[45,46] Acute respiratory illnesses or an anesthetic procedure can easily lead to respiratory insufficiency in the PBS patient, who may have underlying chronic bronchitis from repeated respiratory illnesses. Many patients demonstrate significant restrictive lung disease secondary to musculoskeletal abnormalities such as scoliosis, rib cage abnormalities, and compromised abdominal musculature.[22]

Gastrointestinal Abnormalities

In at least 30% of cases, gastrointestinal anomalies are observed. Most result from incomplete rotation of the midgut, which produces a wide mesentery, resulting in increased bowel mobility with intestinal malrotation, volvulus, atresias, and stenosis.[47,48] Splenic torsion has also been reported due to abnormal mesenteric fixation.[49,50] Omphalocele, gastroschisis, and anorectal abnormalities (Fig. 32-3) have also been reported.[51-55] With a limited ability to generate intra-abdominal pressure, constipation becomes a lifelong problem and leads to acquired megacolon.[41]

Orthopedic Abnormalities

Orthopedic abnormalities, ranging in incidence from 30% to 45%, are second in frequency to those of the genitourinary tract and abdominal wall. Many of these abnormalities result from the compressive effects of oligohydramnios. Some believe that the musculoskeletal defects result from the abnormal mesenchymal development at 6 weeks' gestation.[56] However, Green and associates pointed out that, because many of the deformities are unilateral, oligohydramnios is the most likely etiology.[57] Dimpling of the lateral aspect of the knees is a common finding in oligohydramnios. Oligohydramnios may also result in talipes equinovarus (26%), hip dysplasia (5%), and congenital scoliosis (4%).[41] It has been proposed that a distended bladder impinging

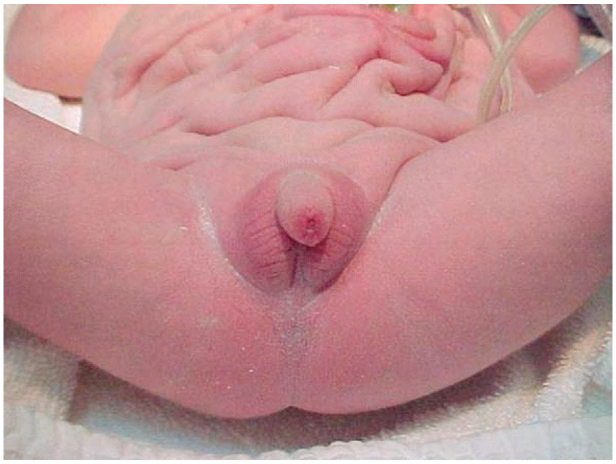

Figure 32-1 Newborn with prune-belly syndrome and imperforate anus. (Courtesy of L. Ruiz.)

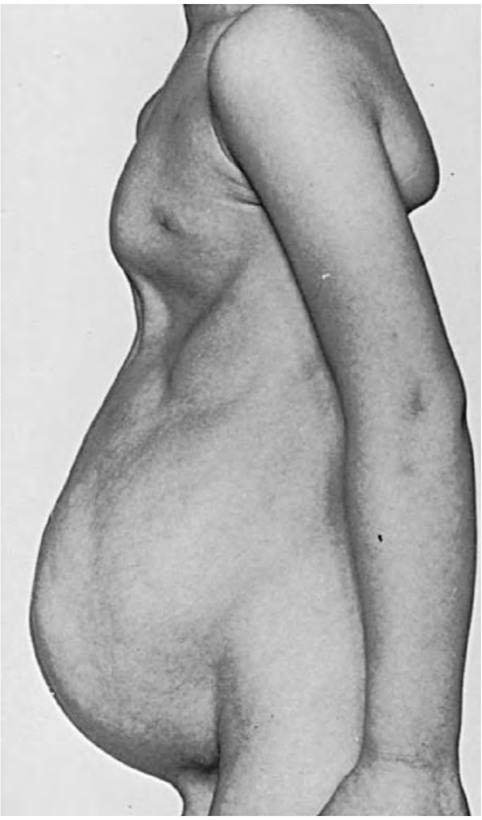

Figure 32-2 Older child with prune-belly syndrome, showing the absence of wrinkling, the "pot-belly" appearance, and the consequent deformity of the lower ribs. (From Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, Chapter 118, Fig. 7.)

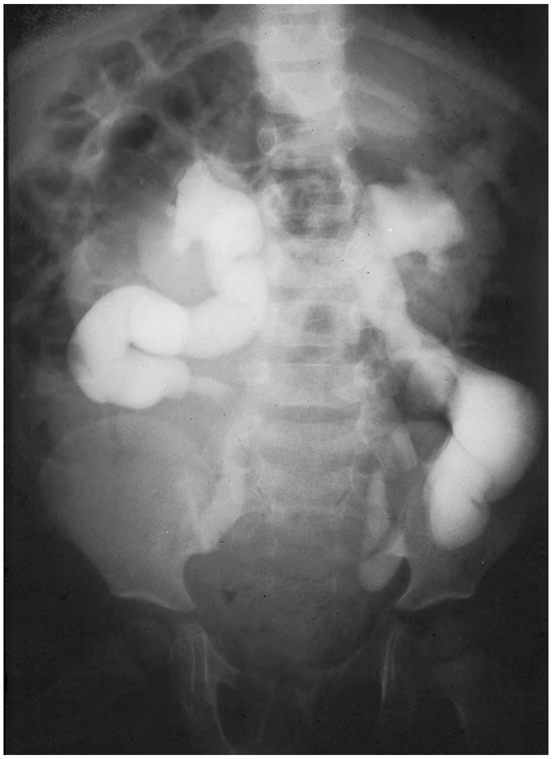

Figure 32-3 Excretory urogram of a patient with prune-belly syndrome. Note ureters displaced laterally and calyces relatively well preserved. (From Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, Chapter 118, Fig. 2.)

on the external iliac vessels may compromise the blood supply to the lower extremities and, in severely affected cases, result in lower extremity hypoplasia, absence, or amputation.[57,58]

Genitourinary Anomalies

Kidneys

The spectrum of renal abnormalities extends from normal renal parenchyma to dysplasia. The more severely dysplastic kidneys are generally associated with bladder outlet obstruction in which there has not been decompression through a patent urachus.[59] Dysplasia is present in 50% of cases; however, it may vary in degree and laterality.[20,60] Renal dysplasia in PBS of the Potter type II and IV varieties are seen. The Potter type II variety with few nephrons and parenchymal disorganization is more indicative of a renal mesenchymal defect, whereas the Potter type IV with cortical and tubular cysts is associated with outlet obstruction.[61]

The renal collecting system is characteristically dilated, often to a severe degree (Fig. 32-3). The degree of dilation, however, does not correlate with the degree of renal dysplasia. Calyceal morphology may be well preserved even in the face of massively dilated ureters and renal pelves.[62] Ureteropelvic junction obstruction can occur on a primary or secondary basis; however, nonobstructive hydronephrosis is the rule.[63] It is renal infection, rather than obstruction, that poses the greatest risk to renal function.

Ureters

The ureters are typically dilated, tortuous, and redundant (see Fig. 32-3). The proximal (upper) portions of the ureters are usually less abnormal than the distal segments, although massive dilation and stenosis can occur at any level. Typically, histologic sectioning demonstrates a lack of smooth muscle cells and an increase in fibrous connective tissue. There are more normal-appearing smooth muscle cells in the proximal segments.[20,64] This fact is critical when ureteral reconstruction is undertaken. The ratio of collagen to smooth muscle cells in prune-belly ureters is elevated, especially in refluxing ureters.[65] A decreased number of thick and thin myofibrils seen on ultrastructural examination is thought to contribute to the poor peristalsis.[20,62]

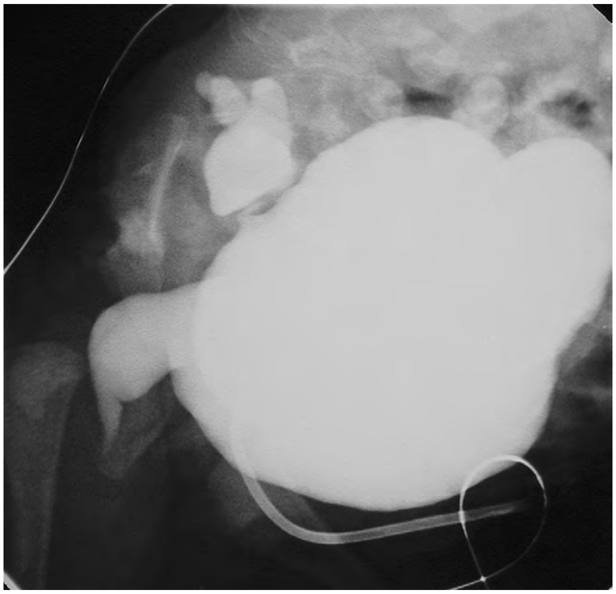

Figure 32-4 Voiding cystourethrogram in a child with prune-belly syndrome demonstrates urethral atresia, urachal diverticulum, and right vesicoureteral reflux.

Vesicoureteral reflux is present in 75% of children with PBS.[62,66] (Fig. 32-4). Obstruction is not common but has been reported both at the ureteropelvic and the ureterovesical junctions.[34,61,67]

These large ureters may have ineffective peristalsis because of poor ureteral wall coaptation. The ureteral conduction wave reaches a reduced smooth muscle cell population that has poor contractile potential because of reduced myofibrils, often separated by patches of collagen; the resulting bolus of urine reaches more dilated ureteral segments as it progresses towards the bladder.[41] This can be seen fluoroscopically as ineffective peristalsis, resulting in upper tract stasis that may lead to infection.[6,42]

Bladder

The bladder usually appears massively enlarged, with a pseudodiverticulum at the urachus (see Fig. 32-4). The urachus is patent at birth in 25% to 30% of children[21,61,68] Histologically, the bladder has an increased ratio of collagen to muscle fibers in the absence of obstruction.[69] The wall is smooth, unlike that seen in obstructed bladders. The pelvic distribution of ganglion cells has been shown to be normal.[42,70] Smooth muscle hypertrophy is seen in the obstructed prune bladder.[71] As noted by Williams and Burkholder, Stephens had demonstrated that the trigone is splayed, with the ureteral orifices displaced laterally and superiorly, possibly contributing to the high incidence of reflux.[6]

On voiding, the bladder neck opens widely into a dilated prostatic urethra (Fig. 32-5). Urodynamic assessment usually shows normal compliance; however, there is a delayed first

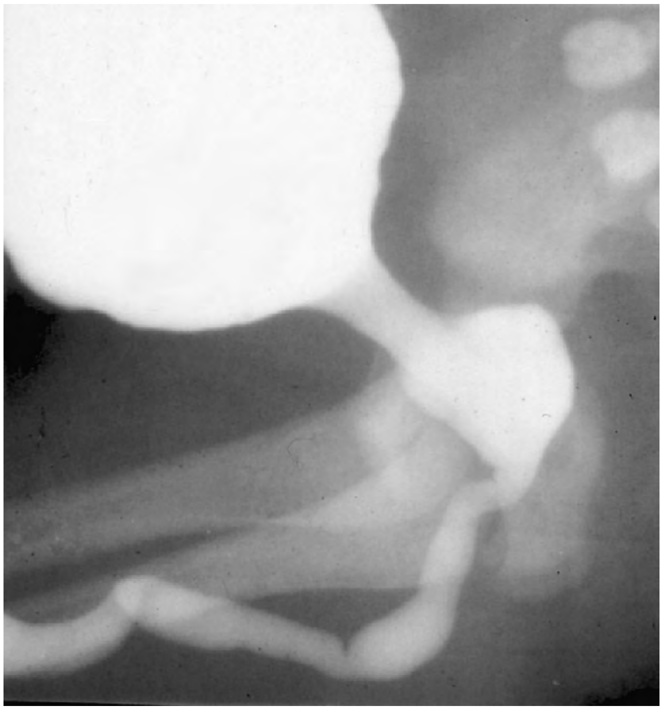

Figure 32-5 Voiding cystourethrogram of a child with prune-belly syndrome demonstrates the prostatic urethral enlargement that results from a hypoplastic urethra. (From Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, Chapter 118, Fig. 4.)

sensation to void and a very large capacity.[72] The ability to empty the bladder is variable, with some emptying well and others carrying a significant postvoid residual. This variability is thought to be based on a relative outlet obstruction and a variable ability of the bladder to generate sufficient pressure with a detrusor contraction. If the relative outflow resistance prevents effective bladder emptying, the term *unbalanced voiding* is used.[72,73] Despite these limitations, about 50% of PBS patients void spontaneously with normal voiding pressures, normal flow rates, and low post-void residuals.[42,73] However, as Kinahan and coworkers demonstrated, deterioration of balanced voiding can occur and can result in significant postvoid residuals, emphasizing the need for periodic assessment.[73]

Prostate and Accessory Sex Organs

The dilation of the posterior urethra is a result of prostatic hypoplasia, probably caused by abnormal mesenchymal-epithelial development.[21] Histologically, there are few prostatic cellular elements, with a reduction of both epithelial and smooth muscle cells and an increase in connective tissue cells.[21,67,74] Various obstructive lesions of the distal posterior urethra have been described, such as urethral atresia, valves, urethral stenosis, urethral membrane, and urethral diverticulum, and are thought to occur in 20% of cases.[24] Stephens[20] described an angulation of the urethra during voiding, which he referred to as a type IV valve, that results from lack of prostatic parenchymal tissue. Prostatic hypoplasia, the etiology of which is controversial, is thought to be a factor in the ejaculatory failure of PBS patients.[75] The vas and seminal vesicles are often atretic, although either may be dilated or thickened.[21] The epididymis may be poorly attached to the testis, as is seen commonly in abdominal undescended testes. There also may be lack of continuity between the efferent ductules and the rete testis. Ejaculation usually occurs in a retrograde fashion because of the incompetent bladder neck.

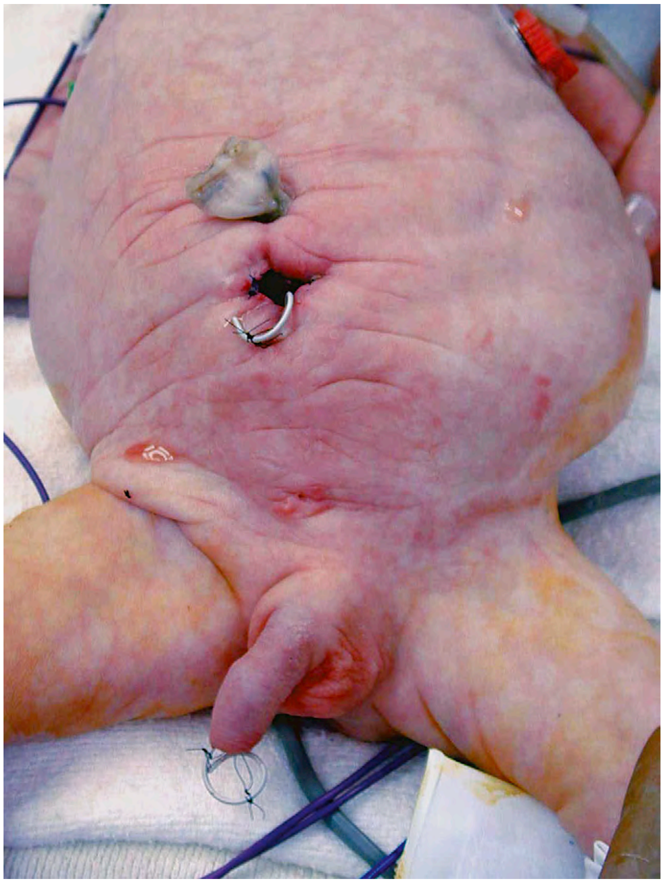

Figure 32-6 Patient with prune-belly syndrome and urethral atresia. Note vesicostomy and double-J stent through the urethra and vesicostomy for progressive dilation. (From Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, Chapter 118, Fig. 9.)

Anterior Urethra

The anterior urethra of the PBS child is usually normal, but several anomalies have been reported, with the most common being urethral atresia and megalourethra.[76,77] Unless it is associated with a patent urachus, urethral atresia can be lethal (Fig. 32-6). It has been postulated that urethral atresia or microurethra occurs because the urethra is unused rather than malformed. Spontaneous bladder rupture with fistula formation has also been reported.[78]

PBS is associated with two variations of megalourethra.[79,80] The fusiform type is a deficiency of the corpus cavernosa as well as the spongiosum, whereas the scaphoid variety is a deficiency of the spongiosum only, with preservation of the glans and corpora cavernosa (Fig. 32-7). With the scaphoid variety, the ventral urethra dilates with voiding; with the fusiform variety, the entire phallus dilates with voiding. The fusiform variety is thought to result from a mesenchymal deficiency of the urethral folds, whereas the scaphoid variety results from a mesenchymal deficiency of the urethral supportive tissues.[81] Megalourethra is more commonly seen in PBS than in any other syndrome.[82] Transient in utero obstruction of the junction between the glanular and penile urethra has been proposed to cause megalourethra.

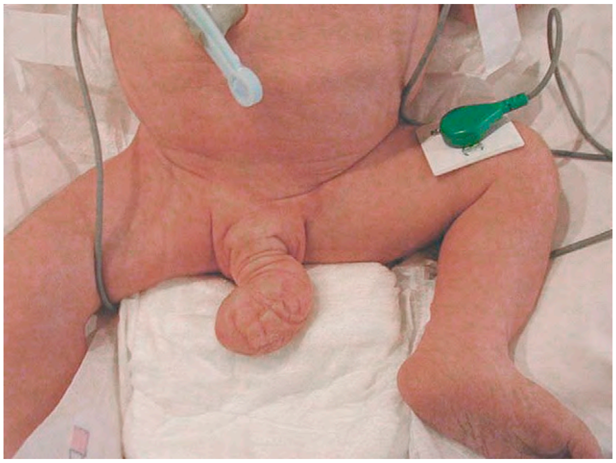

Figure 32-7 Prune-belly syndrome with scaphoid megalourethra. (Courtesy of L. Ruiz.)

Testes

The most typical finding is bilateral intra-abdominal testes lying over the iliac vessels. Although mechanical forces such as a distended bladder and intra-abdominal pressure have been implicated in maldescent of the testes,[83,84] the fact that some patients with the typical urinary tract and abdominal musculature anomalies (termed *pseudo-prune* patients) may have descended testes raises some doubt as to a purely mechanical etiology.

Pak and colleagues[85] compared the histology of the testis in PBS patients with that of non–prune-belly intra-abdominal testis as well as age-matched controls. They found no difference in germ cell counts, spermatogonia, or Leydig cells between PBS and non-PBS patients with intra-abdominal testes. However, germ cell counts in PBS patients younger than 1 year of age were similar to those of age-matched controls, implying that the environmental state of the abdomen is a major factor in their later spermatogenic potential.[22,42] This mirrors the finding by Nunn and Stephens of normal germinal epithelium in fetal and newborn PBS testes.[42] Alternatively, Orvis and associates[86] noted a decreased number of spermatogonia and Leydig cell hyperplasia in fetal PBS testes, implying an intrinsic testicular abnormality. Azoospermia was found in adult PBS patients, and no patient with PBS has been reported to have fathered a child.[87] More recently, Ross and associates[88] documented paternity in three adults with classic PBS, which was achieved by sperm retrieval techniques and intracytoplasmic sperm injection (ICSI). The infertility is thought to be caused by a combination of testicular histologic abnormalities, structural defects of the ducts, and prostatic abnormalities.[89]

Three cases of testis tumor have been reported.[90-93] Massad and coworkers[93] described histologic testicular patterns similar to intratubular germ cell neoplasia in three infants. Although the risk of malignancy may be relatively low considering the lack of germinal epithelium,[94] it is clear that placement of the testis in the scrotum and long-term follow-up are necessary to potentially reduce the risk of testicular malignancy and enhance detection.

PRESENTATION

Prenatal Diagnosis and Management

Fetal hydronephrosis can be diagnosed accurately in the second trimester and is present in approximately 1% of all pregnancies. However, the cause of the hydronephrosis cannot be accurately determined in all cases. Elder[95] estimated that the accuracy of determining the etiology of fetal hydronephrosis varies from 30% to 85%. In particular, PBS manifests prenatally with findings similar to those of other causes of bladder outlet obstruction (Figs. 32-8 and 32-9), such as posterior urethral valves, or megacystis megaureter syndrome.[96] Although the accurate diagnosis of PBS has been made as early as 11 to 14 weeks' gestation,[97,98] the classic findings of hydroureteronephrosis, a distended bladder, and an irregular abdominal circumference are not consistently seen at 30 weeks.[99-102] Early fetal ascites has been suggested to correlate with PBS.[103] It is imperative to remember that most patients with PBS do not have demonstrable urinary obstruction and that the degree of hydroureteronephrosis does not correlate with the postnatal renal function.[104]

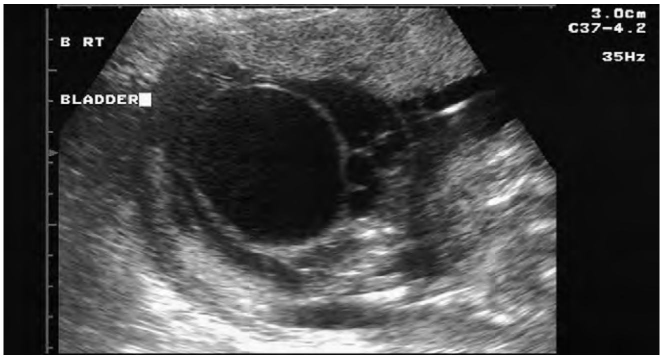

Figure 32-8 Distended bladder with dilated loops of ureter and urinary ascites. (From Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, Chapter 118, Fig. 8B.)

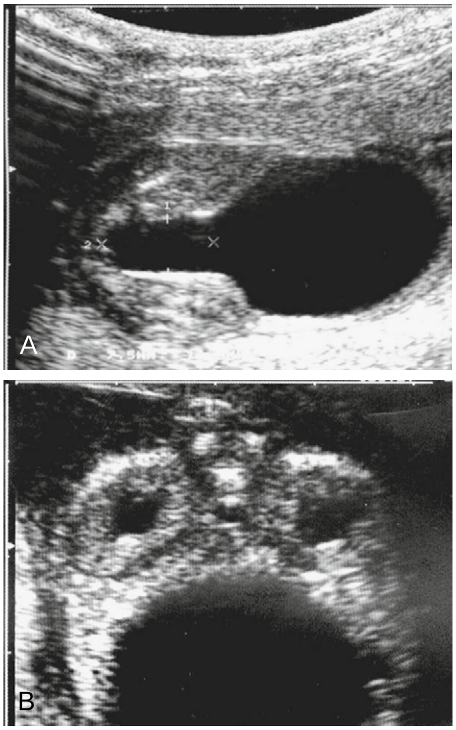

Figure 32-9 **A,** Prenatal ultrasound scan demonstrates distended bladder with dilated proximal urethra. **B,** Echogenic renal parenchyma bilaterally with moderate hydronephrosis. (Courtesy of L. Ruiz.)

Table 32-2 **Spectrum of Prune-Belly Syndrome**

Distinguishing Characteristics	Category Classification
Oligohydramnios, pulmonary hypoplasia, or pneumothorax; may have urethral obstruction or patent urachus	I
Typical external features and uropathy of the full-blown syndrome but no immediate problem with survival; may have mild or unilateral renal dysplasia; may or may not develop urosepsis or gradual azotemia	II
External features may be mild or incomplete; uropathy is less severe; renal function is stable	III

From Woodard JR. Prune belly syndrome. In: Kelalis PP, King LR, Belman AB, eds. *Clinical Pediatric Urology*. Philadelphia: WB Saunders; 1985:805-824.

Whereas some have recommended in utero intervention for relief of urinary tract dilation and oligohydramnios,[18,103-107] others have recommended termination of pregnancy.[108] It is difficult to justify advocating pregnancy termination in light of our inability to precisely diagnose the cause of prenatal hydronephrosis and to predict postnatal renal function based on the degree of urinary tract dilation, except in those rare cases of early and severe oligohydramnios. Prenatal intervention has been applied to PBS with no proven benefit in terms of postnatal renal function.[109-113] The only circumstances in which prenatal intervention may be justified are those rare situations of urethral atresia with progressive oligohydramnios[78,114,115] or when decompression of the urinary tract is necessary to prevent dystocia.[104]

Neonatal Presentation

The appearance of the abdominal wall immediately suggests the diagnosis of PBS (see Fig. 32-1), whether or not the diagnosis was suspected prenatally. It should be remembered that other associated abnormalities, such as cardiac or pulmonary, often should take precedence over the urinary tract, because in the absence of true bladder outlet obstruction, as seen with urethral atresia, the hydroureteronephrosis is not life-threatening.

Spectrum of Disease

With the number of variable anomalies present in PBS, it is understandable that there is a wide spectrum of clinical presentations. Three major categories of presentation in the neonatal period were described by Woodard [116] (Table 32-2).

In *category I* are neonates who have experienced marked oligohydramnios as a result of renal dysplasia or severe bladder outlet obstruction or both, with resultant pulmonary hypoplasia and skeletal abnormalities. Most infants with urethral atresia are in this category. The exceptions are those patients with urethral atresia and a patent urachus.[60] Patients in this category who are not stillborn commonly succumb within a few days of life to pulmonary hypoplasia or later to renal failure. Approximately 20% of newborns with PBS die in the perinatal period.[63,66,117] It would be unusual for any urologic intervention in this category of patients to alter the course of events. Simple catheter drainage is all that is justifiable.

Category II demonstrates the full spectrum of the disorder, with moderate or unilateral renal insufficiency and moderate to severe hydroureteronephrosis. Pulmonary hypoplasia is not a prominent feature of this group of patients. The clinical course is that of stabilization of renal function, at normal or somewhat below normal levels, or progressive azotemia. It is in this group of patients that significant controversy regarding management exists.[118]

Category III is composed of patients with mild features of the triad or incomplete forms of PBS. This category comprises the majority of PBS patients in whom hydroureteronephrosis is present to some degree but renal function is well maintained.[119,120] There is no evidence of pulmonary insufficiency. There is little controversy that urologic intervention in this group should be reserved for those patients who demonstrate repeated urinary infections, most likely because of urinary stasis or vesicoureteral reflux, or development of upper tract deterioration.[41] As previously noted, there is poor correlation between the extent of abdominal wall deficit and the degree of hydronephrosis or renal dysplasia. This is also apparent in other variant forms of the syndrome. There are children with markedly dilated urinary tracts who have minimal or no dysplasia and, therefore, normal renal function. The appearance of the abdominal wall or the degree of hydronephrosis may have little bearing on the long-term prognosis of children with PBS.

Incomplete Syndrome

Male patients who may not have all the features of the triad syndrome but share other features are said to have *incomplete syndrome*. Most typically, they lack the typical abdominal wall features but have the common uropathy and cryptorchidism. Because many of these patients go on to renal failure, they require close observation, monitoring, and selective intervention. Bellah and associates[121] reported a relatively high tendency to progressive renal failure in their population of pseudo-prune patients. This finding may be partially attributed to a delay in diagnosis in the absence of the obvious abdominal musculature deficiency and a resultant tendency to present with recurring urinary tract infections.

Adult Presentation

Patients with incomplete forms of PBS, and specifically those who lack the abdominal wall features, may present as late as adulthood with symptoms of renal failure and hypertension.[122,123] Although there have been isolated reports of adults with no history of urinary tract infections, most others who present in adulthood eventually develop urinary infections because of the chronic urinary stasis associated with the syndrome.[124]

Female Syndrome

Five percent of PBS patients are female; most of them have the abdominal wall deficiency and the abnormal urinary tract.[9] Rabinowitz and Schillinger[8] reported female patients with the typical abdominal wall deficit and a normal urinary tract. In the series by Reinberg and colleagues, bladder outlet obstruction was commonly seen, along with a 40% occurrence of anorectal anomalies; like male with PBS, 40% did not survive the newborn period.[9]

MANAGEMENT

Postnatal Evaluation and Management

The initial evaluation of the newborn with PBS requires a team consisting of a neonatologist, a nephrologist, and a urologist. As dictated by the findings, other specialists, particularly a cardiologist, may be indicated. Early orthopedic evaluation is also warranted. The major initial concern is the management of cardiac and respiratory issues. An immediate chest radiograph is necessary to exclude common associated pulmonary abnormalities such as pneumothorax, pneumomediastinum, and pulmonary hypoplasia, which often occur as a result of oligohydramnios.[125] Early urologic intervention is indicated only for those neonates with evidence of bladder outlet obstruction, in whom a percutaneous suprapubic tube can be inserted in the neonatal intensive care unit.

Initial evaluation of renal function and urinary tract status is important but must be tempered by understanding of transitional neonatal physiology. Although an initial creatinine determination is important in establishing a baseline, it may be more reflective of the mother's renal function, and the trend in creatinine levels over the course of the early postnatal days or weeks is much more predictive of long-term renal function.

Analysis of serum blood urea nitrogen (BUN) and electrolytes is needed to assess for the potential systemic acidosis and electrolyte imbalances that may be seen in renal insufficiency. It has been shown in many reports that a baseline creatinine concentration of less than 0.7 mg/dL is predictive of adequate renal function through childhood, in the absence of repeated results from pyelonephritis.[33,126,127]

Early renal and bladder ultrasonography, once the newborn has been stabilized, is necessary to assess the renal parenchyma (thickness, density, and presence or absence of cortical cysts) and the degree of urinary tract dilation.

Avoidance of urinary infection is essential in light of the urinary stasis and the often-compromised baseline renal function. Circumcision is advisable in the absence of a structural penile abnormality, to reduce the risk of infant urinary tract infections. Prophylactic antibiotic therapy is recommended, especially before urinary tract instrumentation, including the initial voiding cystourethrogram (VCUG). Although instrumentation without a defined purpose that might alter management should be avoided, a VCUG to assess the bladder outlet and bladder emptying ability, especially in the face of renal insufficiency, is warranted.[41] The VCUG is needed in neonates with renal insufficiency to rule out bladder outlet obstruction as the etiology (versus urinary stagnation). In up to 70% of children with PBS, vesicoureteral reflux is diagnosed.[62,66] Any instrumentation should be carried out with strict attention to sterile technique to reduce the risk of inoculation of a static urinary system. An early VCUG can be avoided if renal function is normal and there is evidence of adequate bladder drainage per urethra or a patent urachus.

As noted, neonates can be categorized based on their spectrum of disease (see Table 32-2). There is little disagreement on the management of PBS patients in category I. There is no evidence that anything beyond supportive care is justifiable. In particular, intervention of the urinary tract is not indicated beyond simple bladder drainage, as the fate of these patients cannot be altered.[41]

At the other end of the spectrum, patients in category III rarely require urologic intervention for the urinary tract, because they are in a balanced state of hydronephrosis with good, if not normal, renal function. Early in infancy, their cryptorchidism will require correction. Children in this category require regular monitoring of urinary tract dilation (ultrasonography) and renal function (serum creatinine measurements).

Category II patients require individualization of evaluation and management, because they have variable degrees of severity for each of the facets of PBS. However, there is much controversy regarding the appropriate management. Evaluation of renal function, renal drainage, or both is required in those patients with renal insufficiency. Excretory urography, although it provides dramatic images of the urinary tract (see Fig. 32-4), does not provide sufficient information about comparative function. Renal parenchymal function is best assessed by a technetium 99m (Tc^{99m}) dimercaptosuccinic acid (DMSA) renal scan, performed at 4 to 6 weeks of age to prevent difficulties in interpretation due to transitional neonatal physiology. Renal outflow obstruction is best assessed by Tc^{99m}-labeled mercaptoacetyltriglycerine (MAG3), which also provides an assessment of comparative renal function in those patients with massive hydronephrosis and resultant stasis. In the face of poor renal function, assessment of renal outflow obstruction by nuclear scan techniques may be limited; in such cases, selective use of the Whitaker antegrade perfusion test may be helpful.

The impetus for aggressive surgical intervention was initially derived from early observations of the poor prognosis for category II infants as a group. Compilation of the cases reported in the literature between 1950 and 1970 by Waldbaum and Marshall[118] revealed that 86% of the 56 accurately traceable patients had died, with or without surgical intervention. The obvious implication was that a more aggressive approach was necessary to improve the fate of the infant with PBS. With the recognition that infection and progressive renal insufficiency are usually the factors that pose the greatest threat to quality of life and survival, surgical reconstruction to normalize the anatomy and function of the genitourinary tract was advocated. Early retailoring of the urinary system to reduce stasis and eliminate reflux or obstruction included ureteral shortening, tapering, and vesicoureteral reimplantation and reduction cystoplasty. Reconstruction is best delayed until the child is at least 3 months of age, to allow for pulmonary maturation. This approach has been successful in achieving anatomic and functional improvement, as evidenced by stable radiographic studies, stable creatinine values, and a reduced occurrence of infection.[39,63,118,128] In the personal reconstructive experience of one of us (JW), 15 patients have maintained a normal creatinine level, and only 2 have demonstrated moderate renal insufficiency, with follow-up ranging from 2 to 27 years.

An alternative approach of limited surgical intervention has also been applied. Proponents advocate close surveillance with medical management of bacteriuria and surgical intervention only in those patients with proven obstruction or intractable infection. Opinions vary about the management of vesicoureteral reflux in the PBS population, although there is no reason to believe that reflux in this population is any less important and correction of high-grade reflux seems prudent. Success with minimal surgical intervention has been reported.[129-132] Woodhouse and his associates reviewed a series of patients with PBS managed conservatively.[129] Nine of the 11 patients, who were monitored from infancy, remained well except for a few urinary tract infections for periods of up to 24 years. They were said to have normal voiding patterns and normal renal function. Certainly, patients in category III are candidates for this type of management.

The paucity of long-term data for category II patients, the probable variation in assignment of disease severity in the various treatment groups, and the variable natural history of the disease make comparisons of retrospective studies difficult. Spontaneous improvement in ureteral appearance and function may occur with normal growth and elongation of the ureters.[130] Also, some patients with gross abnormalities of the urinary collecting system have survived decades without medical attention.[122,133,134] Yet, progressive uropathy is also well known to occur, and many patients with PBS ultimately require renal transplantation.[135] Controversy will

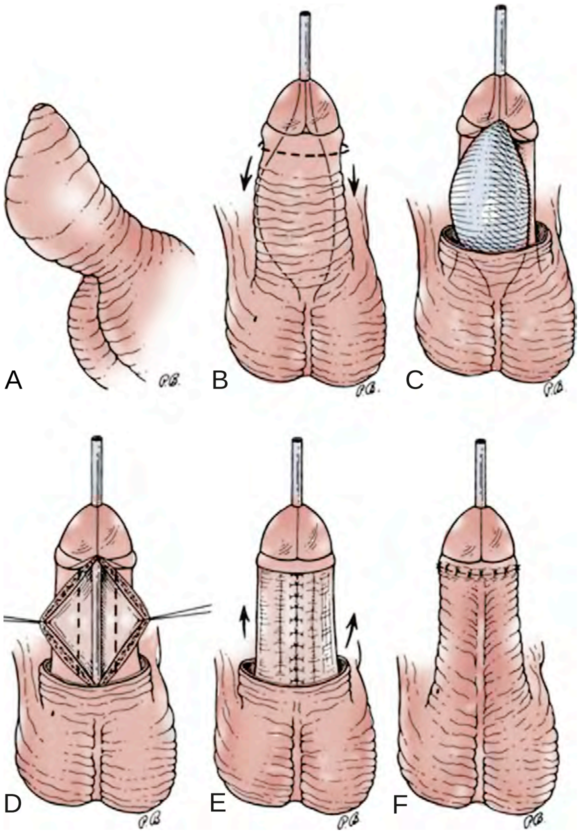

Figure 32-10 **A,** The prepuce is reduced, and a circumcising incision is formed, preserving a mucosal collar. **B,** With a catheter in place to assist with identification of the urethra, the penis is degloved along the subdartos plane. **C,** The involved segment of the urethra is opened longitudinally, and the redundant urethral wall is excised to allow tapering of the urethra over a catheter of approximate size. **D,** The urethra is closed with absorbable running sutures and is bolstered with a second layer of sutures placed in an interrupted fashion if possible. **E,** The penile skin is brought forward, and the excess foreskin is removed with a second circumferential incision. **F,** The penile shaft skin is approximated to the mucocutaneous border. (From Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, Chapter 118, Fig. 10.)

persist regarding category II patients until accurate application of a medical or surgical approach is possible based on distinct clinical features. Dénes and coworkers[136] emphasized the individualization of care in their 17-year experience with 32 patients.

Surgical Management

Surgical management of children with PBS can be divided into three categories: urinary tract reconstruction, abdominal wall reconstruction, and orchidopexy. Urinary tract reconstruction is generally reserved for those children with progressive or severe hydronephrosis, recurrent upper tract infections, true obstructive uropathy, and progressive renal failure. Temporary urinary diversion also has a role in the very young or the very ill child.

Temporary Urinary Diversion

In certain instances, the repeated occurrence of upper tract infections or deterioration of renal function dictates temporary urinary diversion. Although cutaneous vesicostomy usually provides adequate upper tract drainage and decompression, in rare instances more proximal diversion is indicated because of ureteropelvic or ureterovesical junction obstruction. Here, a cutaneous pyeloplasty is advocated rather than proximal ureterostomy, because the former procedure provides the best upper tract drainage and avoids the sacrifice of a normal proximal ureter that might be useful in later reconstruction.

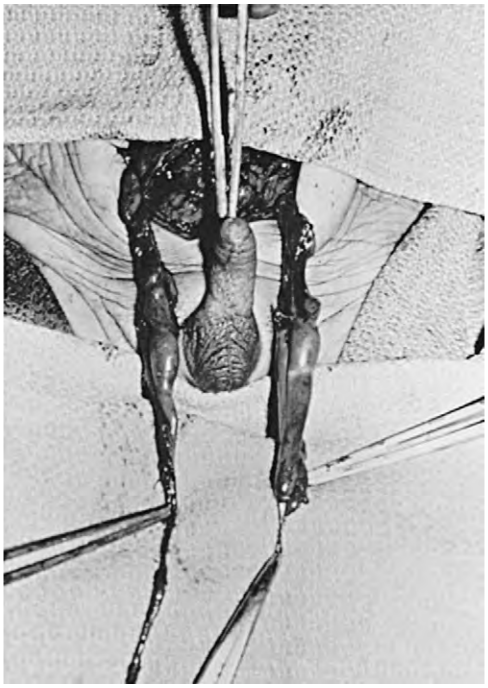

Figure 32-11 Operative photograph showing the ease with which the testes reach the scrotum after neonatal transabdominal mobilization of the spermatic cords. (From Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, Chapter 118, Fig. 11.)

Urinary diversion may be necessary as a temporary measure in children with acute renal failure, urinary sepsis, or bladder outlet obstruction from urethral atresia with limited patency of the urachus.[137] If temporary urinary diversion is indicated, a cutaneous vesicostomy is the procedure of choice. This is best done by the Blocksom technique as described by Duckett.[138,139] If there is a large urachal diverticula, it can be excised at that time. It is advisable to create a larger than normal stoma in the PBS patient, because stenosis is common, most likely because of the decreased intra-abdominal pressure.[140]

Ureteral Reconstruction

Ureteral remodeling remains controversial. It is best undertaken in those children who have demonstrated repeated, nonsuppressible upper urinary tract infections and those with progressive upper tract deterioration. The goal of remodeling is to reduce urinary stasis. The key to success relies on meticulous surgical technique and preservation of the upper few centimeters of proximal ureter for reconstruction. Ureteral reimplantation into the abnormal bladder can be difficult because the creation of a submucosal tunnel is challenging.[141] Woodard's group has demonstrated excellent success in this population with procedures performed in the neonatal period or in the older child.[63,142] However, they no longer recommend such extensive reconstructive surgery before the age of 3 to 6 months.

Internal Urethrotomy

In the absence of urethral atresia, true anatomic obstruction of the urethra is rare in PBS. However, the normal resistance of the urinary sphincter has been implicated in "unbalanced" urethrovesical function contributing to large postvoid residuals. Snyder [72] and Cukier[143] and their colleagues proposed lowering the urethral resistance by internal urethrotomy to improve bladder emptying. In patients studied by urodynamic flow rate profilometry, improved flow rates with reduced residual urine and improvement in the radiographic appearance of the upper tracts were demonstrated.[129] Although sustained long-term success has not been demonstrated, internal urethrotomy should be considered in PBS children with high postvoid residuals, increasing hydroureteronephrosis, or vesicoureteral reflux with recurrent upper tract infections. Williams advocated the use of an Otis urethrotome to achieve a caliber of 24F (7.92 mm) to 30F (9.9 mm) with one or two incisions made anteriorly or anterolaterally,[144] but direct visual urethrotomy would seem preferable and should be performed at the distal end of the prostatic urethra.[145] Internal urethrotomy does not result in incontinence in this population.

Anterior Urethral Reconstruction

On one end of the spectrum of urethral maldevelopment is urethral atresia, sometimes referred to as *microurethra* (see Fig. 32-4). Passerini-Glazel and associates[146] reported good success with progressive gentle urethral dilation. This technique may be utilized in situ or through-and-through if a vesicostomy has been performed (see Fig. 32-6). As reported by Reinberg and

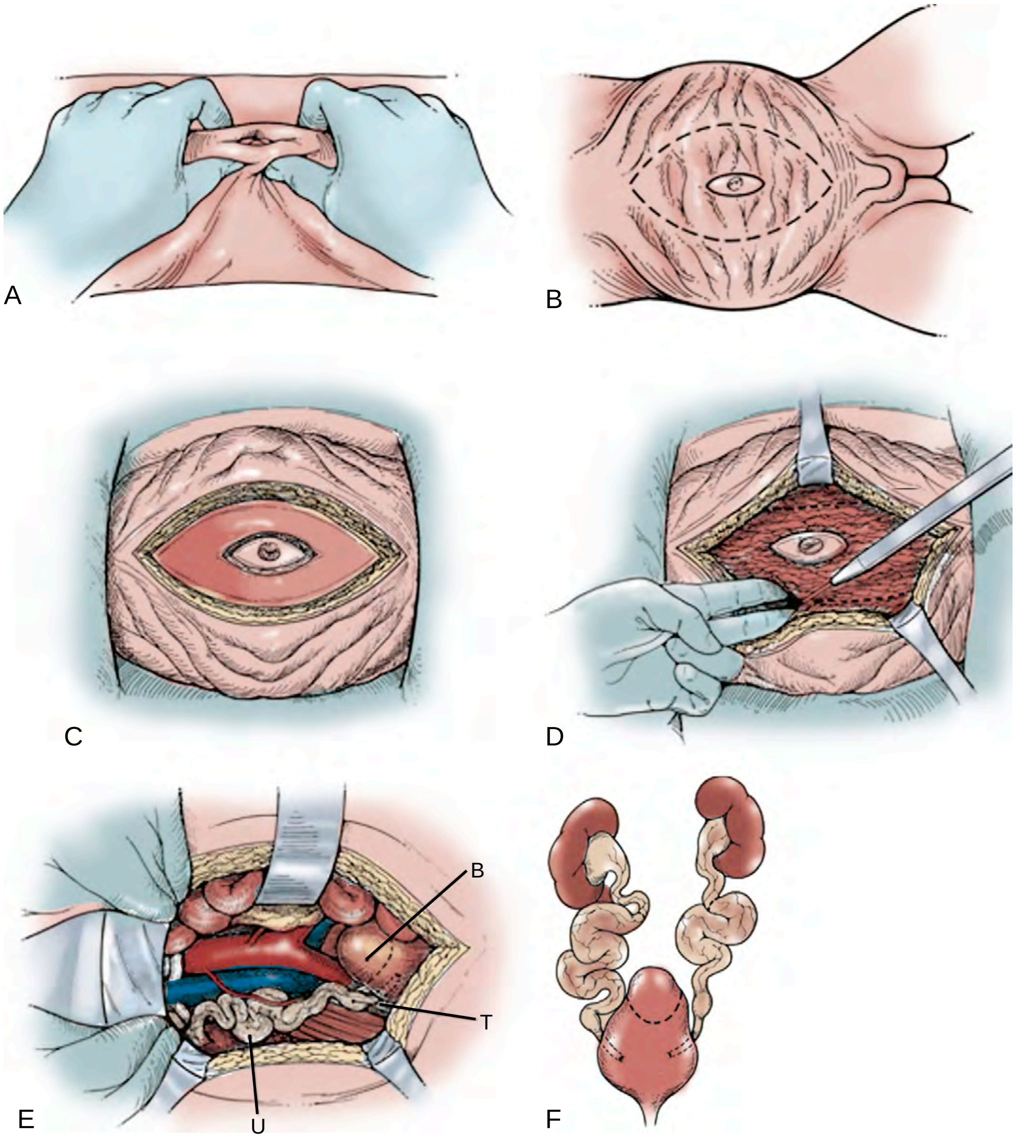

Figure 32-12 Surgical technique for Monfort abdominoplasty and concomitant reconstruction of prune-belly uropathy. **A,** Redundancy is delineated by tenting up the abdominal wall. **B,** Skin incisions are outlined with a separate circumscribing incision to isolate the umbilicus. **C,** Skin (epidermis and dermis only) is excised with electrocautery. **D,** Abdominal wall central plate is incised at the lateral border of the rectus muscle on either side, from the superior epigastric to the inferior epigastric vessels, creating a central musculofascial plate. **E,** Adequate exposure is provided for concomitant transperitoneal genitourinary procedures. **F,** Only the more normal proximal ureter is preserved for vesicoureteral reimplantation, and the urachal diverticulum is excised.

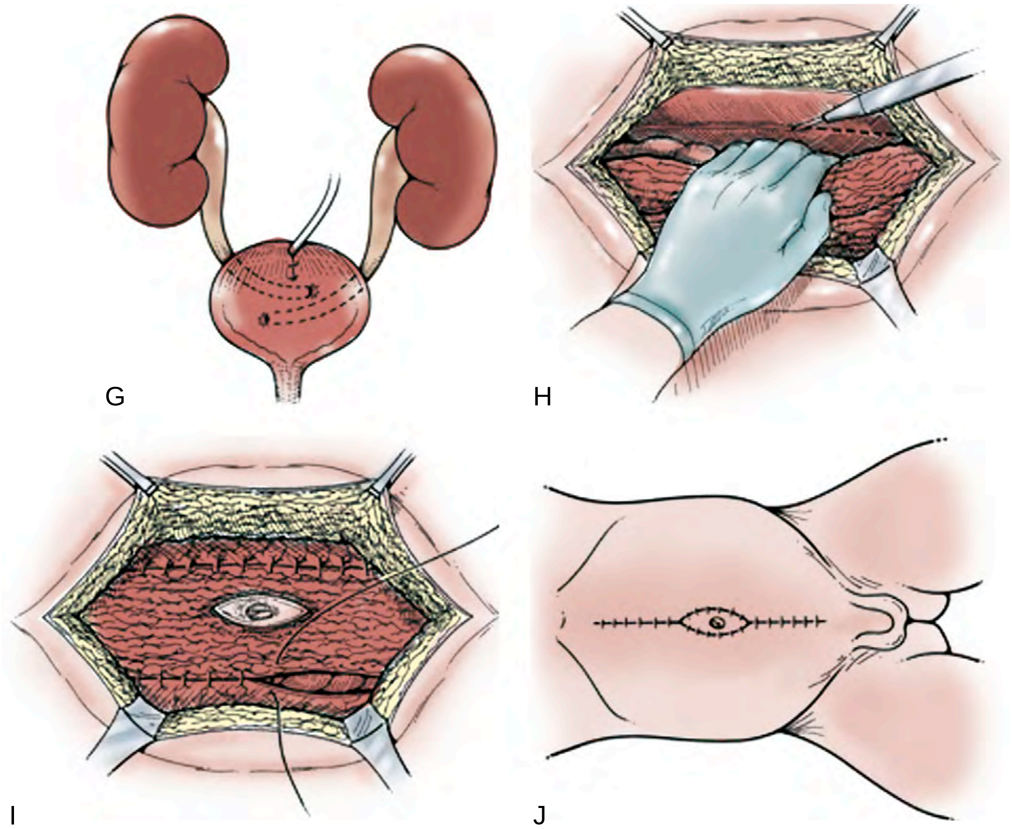

Figure 32-12, cont'd **G,** Transtrigonal ureteral reimplantation is performed with or without ureteral tapering as necessary. The bladder is closed in two layers, and ureteral stents (not shown) and a cystostomy tube are employed. **H,** Abdominoplasty is completed by scoring the parietal peritoneum overlying the lateral abdominal wall musculature with electrocautery. **I,** The edges of the central plate are sutured to the lateral abdominal wall musculature along the scored line. **J,** Lateral flaps are brought together in the midline, with closed suction drains placed between the lateral flaps and the central plate. Skin is brought together in the midline, enveloping the previously isolated umbilicus. (From Woodard JR, Perez LM. Prune-belly syndrome. In: Marshall FF, ed. *Operative Urology*. Philadelphia: WB Saunders; 1996.)

colleagues, however, this technique is not uniformly successful, and a more formal urethroplasty may be required, with skin flaps or grafts or both.[78]

Megalourethra in PBS may be either fusiform or scaphoid.[82] This is best approached with a circumferential subcoronal incision and penile degloving (Fig. 32-10). The redundant urethra can be excised and the urethra reconstructed over a catheter of appropriate size. Alternatively, some of the urethra can be used to reinforce the urethroplasty, because in either form of megalourethra the spongiosum is deficient.

Reduction Cystoplasty

In many PBS patients, poor bladder contractibility leads to incomplete and infrequent emptying, resulting from the complicating urinary stasis and vesicoureteral reflux issues. This has led to the concept of reducing the size of the bladder and remodeling it into a more spherical shape to better direct the contractible forces.[71] A variety of approaches have been proposed, from simple excision of the urachal diverticulum to the excision of redundant mucosa with the creation of overlapping flaps to improve contractibility.[141,147] Over time, however, high bladder capacity and residual volumes seem to recur.[148,149] Therefore, it would seem that reduction cystoplasty is justified only to remove the larger urachal diverticulum or as part of a more extensive internal reconstruction. Intermittent catheterization through the urethra or through an appendicovesicostomy channel is likely to afford better long-term bladder emptying and reduction of residual urinary volumes.[137]

Orchidopexy

The timing of orchidopexy is dictated by our current understanding of the need for early treatment of the undescended testis in non-PBS patients as well as the individual PBS patient's needs for either temporary or reconstructive surgery. Although the fertility potential of the PBS patient is known to be compromised, germ cells are present in the testes of infants with PBS, and the prognosis for normal hormonal function at puberty is excellent. These factors, along with the potential risk of testicular carcinoma,[93,94] justify early orchidopexy. Because the testes are uniformly located in the abdomen, most commonly on a broad mesorchium overlying the iliac vessels,[22] standard inguinal approaches are not usually successful in achieving a satisfactory scrotal position. Four alternative approaches may be considered.

Woodard and Parrott,[63,150] as well as others,[39,66] observed that, if an orchidopexy is done in the neonatal period and up to 6 months of age by a transabdominal approach, adequate spermatic vessel mobilization can usually be achieved for scrotal placement (Fig. 32-11). Transabdominal bilateral orchidopexy at about 6 months of age is currently considered the approach of choice. This approach is often used in conjunction with other abdominal surgeries, such as vesicostomy, urinary

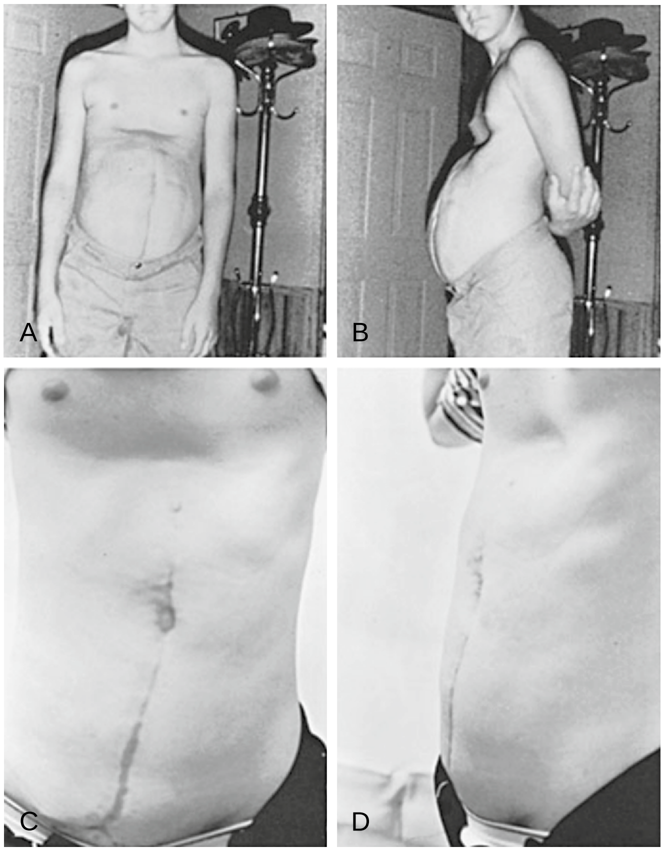

Figure 32-13 **A** and **B,** Anterior and lateral views of the abdomen of a 14-year-old boy who underwent major surgical remodeling of the urinary tract during early infancy with good results. Note typical abdominal configuration. **C** and **D,** Anterior and lateral views of the same boy 1 month after abdominoplasty with the technique described by Monfort. (**A-D,** From Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh Urology*. 9th ed. Philadelphia: WB Saunders; 2007, Chapter 118, Fig. 13.)

tract reconstruction, or abdominal wall reconstruction. In the absence of need for other abdominal surgeries, this procedure can be accomplished laparoscopically.

If successful transabdominal orchidopexy cannot be accomplished in the first few months of life, the other options that may be considered are (1) Fowler-Stephens orchidopexy, [151-54] (2) staged Fowler-Stephens orchidopexy,[155-159] and (3) microvascular autotransplantation.[152,160,161] A meta-analysis by Docimo[162] indicated comparative success rates of 67% and 77% for standard and staged Fowler-Stephens techniques, respectively. In a multi-institutional report of laparoscopic orchidopexy, Baker and coworkers[163] noted a success rate of 81% for a standard Fowler-Stephens approach, compared with 90% for a staged approach. In a long-term follow-up report, Patil and colleagues[164] had a satisfactory outcome with a one- or two-stage Fowler-Stephens orchidopexy.

Reconstruction of the Abdominal Wall

Children with mild degrees of abdominal muscular deficiency may show improvement in the abdominal wall laxity as they mature. However, most others with moderate to severe degrees of abdominal wall laxity are left with a potentially psychologically crippling defect.[165,166] An elasticized corset can improve the external appearance when fully clothed but is inconvenient to use. Although there is general agreement as to the cosmetic benefit of abdominal wall reconstruction, it is controversial whether it improves bladder, bowel, and pulmonary function.[119,167] Smith and colleagues[167] demonstrated improved bladder emptying after abdominal wall reconstruction, but some of their reconstructed patients underwent concomitant urinary tract remodeling as well. Potential effects include a more effective cough and improvement in defecation. The timing of abdominal wall reconstruction should be dictated by the need for other surgical interventions, particularly if upper urinary tract remodeling is necessary. If upper tract remodeling is not anticipated, then the abdominal wall can be addressed at any time. The procedure has been done on patients as young as 6 months of age in conjunction with transabdominal orchidopexy.[145] However, if it is done in infancy, one must be prepared to provide respiratory support for the infant postoperatively for a period of time. Of the methods described in the following paragraphs, the consensus currently is that the Monfort and Ehrlich techniques provide the best functional and cosmetic results.

Randolph and coworkers[39] first popularized a technique for abdominal wall reconstruction based on electromyographic mapping, which indicated that the infraumbilical regions are typically the most severely affected area of the abdomen, whereas the lateral and supraumbilical regions are usually least affected. In their technique, a transverse incision is made from the 12th rib to the pubic symphysis to the opposite 12th rib with a full-thickness removal of the skin, lower abdominal musculature, and peritoneum; the healthy fascia is then approximated to the anterior iliac spines, pubic tubercle, and inferior fascia. Although this technique is successful in establishing a waistline, lateral abdominal bulging often persists. Of the 16 patients reported, 9 had excellent cosmetic results, and there was some residual protuberance in 7.[66]

The technique described by Ehrlich and Fine uses a vertical midline incision and allows for preservation of the umbilicus on a vascular pedicle from the inferior epigastric artery.[165,168] The skin and subcutaneous tissues are elevated off the muscle and fascial layers, and an overlapping, pants-over-vest, advancement of each side to the contralateral flank is performed, preserving the less affected lateral muscles and fascia.

Monfort and associates[169] described a technique that is vertically oriented, similar to that of Ehrlich's approach except that an elliptically oriented incision is used to isolate the redundant skin. The incision extends from the tip of the xiphoid to the pubis. A second incision is made around the umbilicus to preserve it in situ (Fig. 32-12). The skin and subcutaneous tissue are dissented off the attenuated fascia and muscle, with the dissection extending laterally to the anterior axillary line. Vertical fascial incisions are made lateral to the superior epigastric arteries, leaving a central fascial bridge. If intra-abdominal surgery is necessary, excellent exposure of the urinary tract or abdominal testes is afforded through these lateral fascial incisions. The lateral fascia is then advanced over the central fascial bridge from both sides, alleviating the redundancy and increasing the thickness of the abdominal wall (Fig. 32-13).

Furness and coworkers[170] described a modified midline approach that involves less abdominal wall dissection and avoids entering the peritoneum; this may be useful if intra-abdominal surgery is not planned. A recent modification of the Monfort technique uses laparoscopy to protect the abdominal contents.[171]

LONG-TERM OUTLOOK

The nadir creatinine concentration during infancy has proved to be a useful predictor of long-term renal function. If the nadir value is less than 0.7 mg/dL, renal function tends to be stable during childhood unless there is further renal compromise from pyelonephritis.[33,126,127] The importance of urinary tract monitoring by periodic cultures and prompt treatment of urinary tract infections cannot be overemphasized. Unfortunately, the risk of infection is constant in the setting of urinary tract dilation and stasis.

As many as 30% of patients, typically those with impaired renal function at initial evaluation, develop chronic renal failure during childhood or adolescence.[33] Renal transplantation is necessary for these patients to ensure normal growth and development, and success with transplantation in PBS patients can be expected to equal that in other age-matched groups.[135]

Normal growth can be expected in most of the patients with normal renal function, although growth retardation in the absence of renal compromise was observed in one third of the patients in one series.[33] A normal pattern of secondary sexual development can be expected.[87] Although primary fertility is not expected in the PBS population, fertility with assisted reproductive techniques may be feasible in those who have had successful early orchidopexy.

The overall outlook for the PBS patient, both for survival and for quality of care, has improved considerably, largely through advancements in medical, surgical, and urodynamic management. The key to management is individualization of care, because some of these patients require major urologic reconstruction, whereas others need little or no reconstruction. Long-term surveillance of the urinary tract is essential, because the functional dynamics can change over time.

REFERENCES

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PART V

INFRAVESICAL URINE FLOW IMPAIRMENTS

CHAPTER 33

POSTERIOR URETHRAL VALVES

Clare E. Close and Michael E. Mitchell

The fetal bladder cyclically fills and empties from early in development. This action provides stretch forces on the components of the developing bladder wall to produce a compliant organ that can store urine at low pressures and empty effectively. With fetal bladder outlet obstruction by posterior urethral valves (PUV), the developing bladder must carry out pressure work to empty. Normal cycling does not occur, and the bladder wall becomes thickened and noncompliant. As a result, high intravesical pressures develop and are transmitted to the upper tracts, resulting in ureteral dilation, urinary stasis, and parenchymal compression. The elevated upper tract pressures further damage renal parenchyma that may be primarily abnormal. In addition to the insult to the bladder and upper tracts, the elevated voiding pressures cause distention of the prostatic urethra and distortion of the bladder neck and developing external urinary sphincter. So devastating is this constellation of abnormalities that those fetuses with the highest grades of obstruction often do not survive in utero. Historically, severe PUV that remained undetected after birth resulted in urinary sepsis and even death in infancy. Over the last half-century, a variety of surgical interventions, together with improvements in medical management of infant sepsis, have allowed many infants to survive, only to face the continued problems of progressive renal failure and inadequate bladder function.

Today, most infants with PUV are diagnosed in utero, allowing ablation of the urethral obstruction in the first days of life. Although underlying primary renal dysplasia cannot be altered by postnatal intervention, bladder function can often be preserved, thereby avoiding the cascading decline in renal function associated with persistent high bladder pressures. In order to maximize the long-term health of children with valves, it is essential to understand the management issues from the time of antenatal diagnosis through infancy, potty training, and adolescence. Appropriate diagnosis, treatment, and follow-up can result in improved long-term outcomes for the population with this difficult problem.

ANATOMY OF POSTERIOR URETHRAL OBSTRUCTION

In 1919, Hugh Hampton Young and his associates published their historic description of PUV. This classification is still widely accepted, although the description was based on a small number of cases and included adult patients who had previously been instrumented. The most common type of obstruction according to the Young classification is *type I valves,* which lie as fins of mucosal tissue that radiate from the urethral crest of the distal verumontanum and sweep across the urethral lumen to fuse anteriorly.[1] Young *type III valves* are obstructing diaphragms that lie in a transverse plane to the urethral lumen and originate distal to the verumontanum, near the bulbomembranous junction. The openings in the type III diaphragm valve vary in size and location. *Type II valves,* rarely mentioned in the literature, are mucosal folds that radiate from the proximal aspect of the verumontanum and extend cephalad to the bladder neck.[1] Among the original 21 valve cases described by Young and colleagues in 1919[1] and Young and McKay in 1929,[2] there were only 2 type II valves. Later, type II valves were described in patients with voiding abnormalities, but their association with abnormal urethral or bladder function is not documented. Both Pieretti[3] and Hendren[4] found patients with simultaneous type II and type I or III valves, perhaps suggesting that the type II lesion results from a more distal obstruction.

The Young classification of valves has been challenged by several urologists, who have argued that prior instrumentation, inadequate direct endoscopic visualization, and distortion of the anatomy at postmortem examination tended to make the Young classification incorrect. Indeed, only 8 of Young and associates' 21 patients were examined endoscopically. Few can argue that modern videoendoscopic techniques allow a more rigorous assessment of urethral anatomy. Postmortem and endoscopic data suggest a diaphragmatic configuration in all valves that is iatrogenically altered by urethral instrumentation.[5-7] Robertson and Hayes[6] unroofed the anterior urethral wall in 17 formalin-fixed postmortem specimens and found an obstructing diaphragm with a posterior opening, rather than two valve leaflets, in all cases. In a prospective endoscopic study, Dewan[5] evaluated infants with suspected urethral obstruction prior to any other urethral instrumentation. On cystourethroscopy, he found that the obstructing lesions were urethral membranes with a posterior opening. On passage of the cystoscope, the membrane split into two leaflets, as had previously been described by Parkkulainen.[7] Using endoscopic videorecording, Dewan[5] performed a retrospective study of obstructive urethral anatomy. By comparing Young and associates' descriptions with his modern observations, Dewan[5] concluded that lesions described as either type I or type III valves were actually membranes extending from the distal end of the verumontanum with a pinhole opening in the posterior aspect of the diaphragm. In an attempt to provide a simple yet anatomically correct nomenclature for these lesions, Dewan and coworkers[8] advocated replacing the complex Young classification with the unifying terminology *congenital obstructing posterior urethral membranes* (COPUM).

The exact etiology of PUV or membranes has never been established. The prostatic urethra develops from the urogenital sinus by the 8th week of gestational life. The mesonephric ducts and paramesonephric ducts are both absorbed in this region of the vesicourethral canal. The mesonephric ducts develop into the ductus deferens, with the openings (ejaculatory ducts) lying lateral to the verumontanum. The distal paramesonephric ducts form part of the prostatic utricle, a small diverticulum on the verumontanum. The colliculus seminalis or verumontanum forms on the dorsal floor of the prostatic urethra as a result of the elevation of the urethral wall by the expanding ejaculatory ducts and utricle. The ends of the wolffian ducts form the normal urethral crest as they migrate cranially from an anterolateral position in the internal cloaca to a posterior position at the verumontanum.[9] Stephens and associates[10] hypothesized that the wolffian duct orifices in valve patients are initially misplaced and integrate abnormally into the urethral wall to form the obstructing lesion.

URETHRAL VALVES AS A SPECTRUM DISEASE

There is clear clinical evidence that congenital urethral obstruction creates a spectrum disease. The timing and degree of the obstruction and the associated anatomy of the upper tracts are responsible for the range of abnormalities found in valve patients. Anatomic postmortem investigations support the clinical observation that the degree of urethral obstruction is variable, with the anteroposterior dimension of the urethral lumen at the level of the valves measuring from 3 mm to greater than 1 cm.[10]

In 1971, Hendren[4] reported the incidence of secondary anatomic problems in 182 boys with PUV. Significant upper tract changes requiring operation because of infection or scarring occurred in 15% of the patients, with another 15% demonstrating severe hydronephrosis, megaureter, and renal insufficiency. The boys with high-grade urethral obstruction presented early in life with urinary sepsis, renal insufficiency, and pulmonary hypoplasia. Milder obstructive disease was diagnosed in older children who presented with incontinence and urinary tract infections.

Controversy still surrounds the classification of patients with apparent PUV and minimal or no upper tract changes. Hendren[4] reported normal upper tracts with or without associated low-grade vesicoureteral reflux (VUR) or paraureteral diverticula in 70% of the patients. Some believe that this end of the spectrum represents normal urethral variation or the functional obstruction of voiding dyssynergia. In support of Hendren's observations, Pieretti[3] reported mild valves in 41% of 87 boys he treated for PUV. These patients had no upper tract dilation, VUR, or paraureteral diverticula. Diurnal or nocturnal enuresis, urinary tract infection, and urinary frequency were the most common symptoms reported. The resolution of symptoms in 34 of the 36 boys after valve ablation seems to validate the significance of these minor lesions.

Mild cases of PUV have also been described in boys who did not demonstrate the expected radiographic changes in the posterior urethra and bladder on voiding cystourethrography.[11] These patients demonstrated abnormal urodynamic findings suggestive of obstructive damage to the bladder, including high filling and voiding pressures and detrusor instability. The researchers found minor valve leaflets on cystoscopy and reported improvement in symptoms after valve ablation.[11] The contribution of bladder retraining alone in this population has not yet been addressed, leaving intact the argument that these minor urethral lesions exist with functional rather than anatomic obstruction.

CHANGING TREATMENT PHILOSOPHIES OF POSTERIOR URETHRAL VALVES

Although Young is remembered for his valve nomenclature, he should also be recognized for his surgical management of valves. After decades of controversy regarding the management of valve patients, Young and McKay's[2] 1929 recommendation for primary valve ablation is now recognized as the appropriate initial treatment in almost all cases. Young and McKay advocated bladder drainage via a urethral catheter after valve ablation to allow decompression of the distended urinary tract. The duration of bladder drainage was determined by improvement in renal function.

In spite of this early recommendation for primary ablation of valves, treatment by suprapubic catheter drainage became popular. Not surprisingly, the persistent indwelling catheter led to persistent urinary tract infection and poor patient survival.[12] Furthermore, there was concern that total decompression of the bladder could result in a functional ureteral obstruction from compression by the thickened wall of the congenitally obstructed bladder. In 1963, Johnson[13] advocated high urinary tract diversion by temporary cutaneous ureterostomy to decrease the risk of infection in patients with stasis of the dilated upper tracts and poor renal reserve. He argued that ureterostomies provided drainage without tubes and that temporary upper tract diversion could restore bladder function.

A decade later, however, there was evidence in the literature that urinary diversion in valve patients is detrimental to the bladder. Unlike normal bladders or bladders with acquired obstruction, congenitally obstructed bladders develop severe, irreversible hypertonicity when defunctionalized. Lome and coworkers[14] studied the bladders of children undergoing upper tract diversion by ureterostomy. All patients showed normal bladder capacity before the diversion. After diversion, all but one patient with valves showed reduced bladder capacity with poor bladder distention and compliance. Tanagho[15] likewise demonstrated permanent contraction of the bladder in valve patients defunctionalized from 10 to 48 months of age. Two infant patients who were undiverted after 2 and 3 months had return of normal bladder capacity, although bladder compliance and subsequent function were not reported.

In 1970, Hendren[16] also argued against upper tract diversion, reporting that upper tract emptying was often not effective with diversion by ureterostomy and that the popular treatment could result in continued infection and poor patient outcome. He thought that primary valve ablation alone was appropriate for mild cases of obstruction but believed that the massive upper tract dilation and bladder neck hypertrophy associated with severe obstruction necessitated concurrent reconstruction of the megaureter and bladder neck. With or without upper tract reconstruction, Hendren's early definitive valve treatment allowed the bladder to normally fill and empty in the newborn period. This concept, however, was overshadowed by the continued focus on renal function and the belief that upper tract diversion preserves or even improves renal function. In 1990, high diversion was again heralded as the best primary treatment for newborns with

PUV who do not demonstrate a nadir creatinine level of 0.8 mg/dL within 5 days after bladder drainage by urethral catheter.[17] Supravesical urinary diversion was advocated because of concern for persistent obstruction of the ureterovesical junction after relief of urethral obstruction. Arguing against this practice, Tietjen and associates[18] used the Whitaker test to demonstrate fixed ureterovesical junction obstruction in only 4% of renal units in valve patients who had undergone proximal urinary diversion for newborn renal insufficiency. Furthermore, 85% of the patients demonstrated renal dysplasia by biopsy, and 42% of patients had progressed to end-stage renal failure at a mean follow-up of 9 years.

During the 1990s, there was new focus on the true nature of renal insufficiency in patients with PUV. In a review of a large group of these patients, Smith and colleagues[19] found no evidence that urinary diversion delayed the onset of end-stage renal failure. A multicenter study of 178 infants treated for PUV during the first year of life likewise found no long-term renal benefit with proximal urinary diversion.[20] When comparing patients with newborn nadir creatinine levels greater than 1.2 mg/dL treated by early valve ablation alone versus upper tract diversion, Close and coworkers[21] found that progression to end-stage failure occurred with either treatment if renal insufficiency was present after creatinine stabilization at birth. Three of six children in each treatment group required dialysis before age 3 years. Therefore, if there is no hope of reversing the primary renal dysplasia and in utero damage already suffered by these kidneys, diversion can be avoided and treatment can focus instead on the preservation of bladder function.

RENAL PATHOLOGY AND URETHRAL VALVES

Renal insufficiency associated with congenital urethral obstruction may result from either primary renal dysplasia or progressive renal deterioration after birth. Experimental models and clinical cases demonstrate the pathogenesis of renal dysplasia associated with urethral obstruction. Severe obstruction in utero has been theorized to transmit damaging back-pressure to the upper tracts, thereby causing deformation of the developing nephrons. Animal data suggest that *early* obstruction may result in severe upper tract changes. Fetal lamb studies showed that early second-trimester ureteral obstruction resulted in renal dysplasia similar to that seen with severe PUV.[22] Similarly, Beck's[23] experimental work in fetal sheep demonstrated dysplasia occurring with early obstruction, whereas later in utero obstruction resulted only in hydronephrosis.

Henneberry and Stephens[24] supported a competing hypothesis known as the "bud theory" of renal dysplasia. They suggested that aberrant caudal budding of the ureter from the mesonephric duct causes aberrant induction of the renal mesenchyme. In support of this theory, they examined 34 renal units from autopsies of valve patients, with 14 of the 19 patients being younger than 6 months of age. They found a significant positive correlation between lateral trigone placement of the ureteral orifice and the gross renal morphologic changes of hydronephrosis and parenchymal thinning. Histologic evaluation demonstrated lower mean glomerular counts and the most severe degree of dysplasia in renal units with the most lateral ureteral placement. Nevertheless, four renal units with grossly dilated and tortuous ureters demonstrated normal parenchymal development. This finding suggests that the obstruction in these cases may have occurred later in gestation and provides evidence that back-pressure and VUR alone are not responsible for dysplasia. The observation of poor function in the refluxing unit of patients with PUV seems to be very common, more so than in patients who have high-grade reflux without urethral obstruction. This may indicate overlapping pathologies, namely that in utero pressure work combined with primary dysmorphism results in dysplasia and poor function.

There are limited clinical histopathologic data in the literature demonstrating the renal damage associated with urethral obstruction. A series of renal biopsies from valve patients with renal insufficiency and reflux demonstrated histologic changes of obstruction in 60%, dysplasia in 25%, interstitial fibrosis in 25%, and infectious change in 15%.[25] The authors contended that the relatively low incidence of primary dysplasia in their series provided support to the practice of supravesical urinary diversion. However, the patients studied were not newborns, so these findings may reflect secondary or post-developmental influences. In contrast, Tietjen and associates[18] reported renal dysplasia in 85% of renal units from babies treated by proximal diversion for renal insufficiency at birth. Daikha-Dahmane and coworkers[26] analyzed kidney lesions from fetuses demonstrating bilateral urinary tract obstruction and surviving 14 to 37 weeks' gestation. All fetuses older than 20 weeks' gestation showed renal dysplasia with blastema cells, interstitial fibrosis, and an arrest of nephrogenesis. These findings support the irreversibility of obstructive changes occurring early in gestation.

PRESSURE POP-OFF MECHANISMS IN URETHRAL OBSTRUCTION

Hoover and Duckett[27] introduced the concept of pressure pop-offs in the obstructed urinary tract in 1982. They noted preserved contralateral renal function in patients with unilateral reflux into a nonfunctioning kidney. This phenomenon, known as the valves, unilateral reflux, and renal dysplasia (VURD) syndrome, suggests that mechanisms that relieve bladder pressure may have a protective effect on renal function. In addition to VUR, other less common pop-off mechanisms include large bladder diverticula, bladder rupture with urinary ascites, and renal urinary extravasation with urinoma formation.

There is growing evidence that decompressive mechanisms may also affect bladder development. If the bladder is protected from pressure work during development, can its morphology and function be preserved? Chen and associates[28] presented unusual documentation of three different pop-off mechanisms in a surviving infant with severe PUV. In their patient, oligohydramnios, bladder dome perforation, and ascites were diagnosed at 26 weeks' gestation. At 37 weeks' gestation, bilateral urinomas developed. Postnatal evaluation revealed bilateral VUR and a small, dystrophic bladder, but there was no long-term follow-up of bladder function. Kaefer and colleagues[29] reported favorable bladder outcomes in 87% of valve patients with pop-off mechanisms. Rather than the typical thick-walled, trabeculated bladder, patients with upper tract pop-off mechanisms may demonstrate a smooth-walled bladder on voiding cystourethrography (VCUG).

PRENATAL DIAGNOSIS OF URETHRAL OBSTRUCTION

In the developed countries where obstetric sonography is routinely performed, most fetuses with urinary tract dilation are detected prenatally. The sensitivity for detection of obstructive uropathy by prenatal ultrasonography in multiple series was between 90% and 100%. Although in some cases the abnormalities causing obstruction are lethal, most babies can be monitored with sequential ultrasound studies and undergo prompt workup and management after delivery. In many communities, obstetricians and perinatologists refer expectant mothers to a pediatric urologist for prenatal consultation if significant obstructive uropathy is suspected. The consultant must be familiar with the urologic details of prenatal ultrasonography and should understand the limitations of the examination in predicting postnatal diagnosis and outcome.

Prenatal ultrasonography should specifically address renal pelvic anteroposterior diameter, amniotic fluid volume, renal echogenicity, renal cortex thickness, bladder distention, bladder wall thickness, presence of urethral dilation, and evidence of urachal patency. Fetal genitourinary tract screening by ultrasound is possible at 20 weeks' gestation, at which time the kidney is of adequate size for evaluation. A renal pelvic diameter between 4 and 10 mm in the second trimester is considered to represent mild dilation and does not persist postnatally in 97% of cases. A diameter exceeding 10 mm, or the presence of dilated calyces with a pelvic diameter of less than 10 mm, suggests significant pathology and warrants postnatal follow-up.[30,31]

The fetal renal parenchyma should be evaluated for thickness and echogenicity. Renal cortical echogenicity equal to that of the adjacent liver can occur in infants less than 4 months of age with normal kidneys. Echogenicity brighter than liver or spleen denotes underlying renal pathology, although the finding is nonspecific and occurs in glomerular, interstitial, tubular, and vascular renal disease.[32] Cortical cysts in a brightly echogenic kidney are an unmistakable indication of primary renal dysplasia. Cortical atrophy can be seen in association with hydronephrosis and is defined as fetal renal cortex less than 2 mm in thickness.[30]

The fetal bladder is more difficult to assess by ultrasonography. By definition, the bladder wall is considered thickened if it is visible when the bladder is full. The diagnostic reliability of wall thickness is questionable, because the bladder is not always full at the time of the examination. Additionally, wall thickening may not occur until later in gestation and therefore will not be seen on early sonograms.

Amniotic fluid volume is a key feature of the fetal ultrasound study. Oligohydramnios is a decrease in the normal amniotic fluid volume that results in restricted fetal movement or fetal compression.[33] It is often a subjective measurement, graded as mild, moderate, or severe. Although there are many nonurologic causes of oligohydramnios, when it is found in association with increased renal echogenicity and persistent bladder distention, the cause is often PUV.[34] However, most large prenatal ultrasound series show oligohydramnios in fewer than half of the patients in whom PUV is suspected.

If hydroureteronephrosis and persistent bladder dilation are found together, the diagnosis of PUV is suspected, although similar findings may be found in patients with prune-belly syndrome, primary megaureter, or VUR (Fig. 33-1). Because the long-term outcomes for these diagnoses differ significantly, there has been an effort to identify characteristics of the obstetric sonogram that differentiate posterior urethral obstruction from other conditions. Of fetuses monitored for persistent megacystis and hydronephrosis suggestive for valves, 42% to 48% had confirmed posterior urethral obstruction at postnatal diagnosis.[31,35] The findings of increased renal echogenicity and oligohydramnios in addition to hydronephrosis and bladder dilation greatly increase the predictive value of prenatal ultrasonography. Kaefer and coworkers[34] reported PUV in 100% of eight male fetuses demonstrating this constellation of findings.

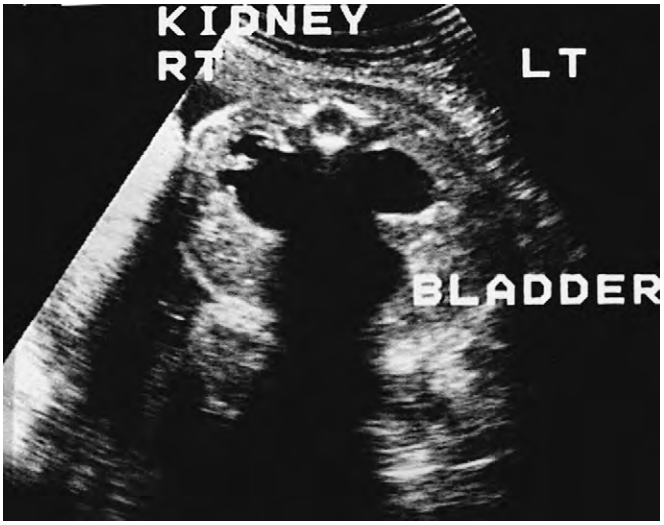

Figure 33-1 Antenatal ultrasound demonstrates bilateral hydronephrosis and dilated bladder. These findings suggest posterior urethral valves. Postnatal evaluation in this infant revealed high-grade vesicoureteral reflux but no evidence of valves.

POSTNATAL DIAGNOSIS OF URETHRAL OBSTRUCTION

All newborn males with a history of significant prenatal hydronephrosis should be evaluated for possible urethral obstruction. Because volume depletion is common in the first 48 hours of life, ultrasound studies obtained during this period can be falsely negative and should be repeated at 1 week of age. The more severe cases of obstruction typically show hydroureteronephrosis, even with relative volume depletion (Fig. 33-2). A common misconception among some pediatricians is that normal voiding guarantees a normal urethra. Although some infants with obstruction have palpable bladder distention or delayed voiding, others have a normal physical examination and regularly wet diapers. A VCUG should be considered before discharge from the nursery if any significant degree of renal collecting system dilation is present on prenatal ultrasonography.

In the infant without prenatal renal imaging, severe urethral obstruction can manifest as abdominal distention from a large full bladder, massive hydroureteronephrosis, or urinary ascites. Patent urachus and retroperitoneal urinoma are other findings that raise the suspicion of bladder outlet obstruction. Newborns with bladder outlet obstruction also present with respiratory distress secondary to pulmonary hypoplasia, severe abdominal distention, or pneumothorax. Other infants with PUV may have a delayed diagnosis made after workup for urinary tract infection, sepsis, acute renal failure, or failure to thrive in the first months of life.

The VCUG remains the "gold standard" for postnatal diagnosis of PUV. Typically, the study is accomplished through retrograde bladder filling via a feeding tube or Foley catheter. A 5F (1.65-mm) feeding tube is preferable to a balloon catheter, which may obscure the diagnosis of nonvalve abnormalities (e.g., ureterocele). Alternatively, some institutions place a 5F suprapubic tube for antegrade bladder filling. The VCUG is best performed by a radiologist versed in pediatric evaluation. The newborn bladder requires cyclic filling during the study to adequately distend the bladder and urethra. Inadequate filling or poor voiding may result in failure to

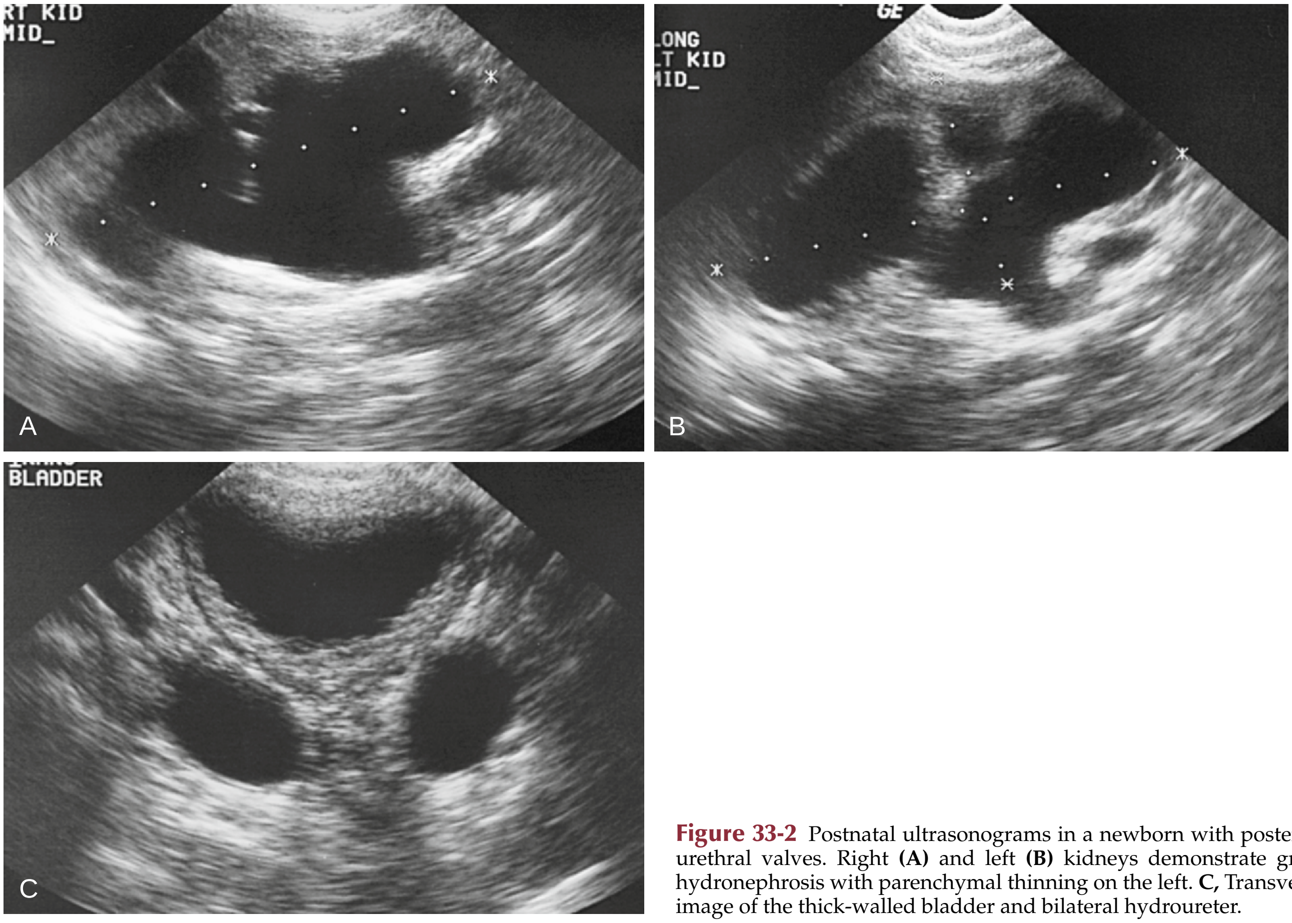

Figure 33-2 Postnatal ultrasonograms in a newborn with posterior urethral valves. Right **(A)** and left **(B)** kidneys demonstrate gross hydronephrosis with parenchymal thinning on the left. **C,** Transverse image of the thick-walled bladder and bilateral hydroureter.

demonstrate VUR or prostatic urethral dilation. The VCUG should be personally reviewed by the urologist, particularly if no obstruction is reported. An oblique view of the urethra in the voiding phase is required to rule out the diagnosis of PUV (Fig. 33-3). On this image, the prostatic urethra is typically elongated and dilated, resulting in elevation of the bladder neck. On the cystogram, the bladder may appear smooth-walled or trabeculated. If there is high-grade reflux, the bladder may not fully distend.

Transperitoneal ultrasonography is reported to be an alternative diagnostic tool that can demonstrate the urethral changes seen with PUV and possibly the obstructive lesion. The limitations of this method include the infrequent voiding in infants and the difficulty of coordinating the study with a sufficient void to demonstrate the anatomic changes.[36]

TREATMENT OF POSTERIOR URETHRAL VALVES IN THE NEWBORN

The initial treatment in a newborn diagnosed with PUV should begin with bladder drainage by urethral catheter, antibiotic administration, and correction of fluid and electrolyte abnormalities. A 6F (1.98-mm) catheter can typically be placed per urethra, with a coudé-tipped catheter or a catheter with a malleable guide facilitating bladder intubation over the elevated bladder neck. Ultrasonography can be used to verify that the catheter is in the bladder and not coiled in the dilated prostatic urethra. Such misplacement is common and often goes unrecognized because the catheter does drain intermittently. The ultimate improvement in renal function and upper tract dilation can be evaluated only after complete decompression of the bladder. If attempts to catheterize the bladder fail, the catheter should be placed under fluoroscopy. Rarely, a very premature infant with urethral obstruction requires bladder drainage through a suprapubic catheter placed with ultrasonographic guidance.

Creatinine measurements during the first days of life reflect the maternal levels and are not indicative of the infant's renal function. Serial creatinine measurements taken 7 to 10 days after bladder drainage establish the newborn preoperative nadir in full-term infants. After this initial period of stabilization, most infants can safely undergo primary ablation of valves.

Endoscopic Valve Ablation in the Newborn

New pediatric endoscopic equipment has drastically changed the surgical approach to valve treatment. Many newborns were treated with vesicostomy in the past only because of the relatively large resectoscopes available. The 8.5F (2.8-mm) resectoscope with a 5-degree lens and cold knife hook working element can be employed in infants as small as 2000 g.[37] Although some surgeons continue to prefer to incise the valves with a Bugbee ball–tipped electrode, the minimal bleeding encountered after cold knife incision of even the fleshiest valves does not require electrocoagulation. Videoendoscopy and cold knife incision allow safe, effective ablation of obstructing urethral lesions without risk of thermal injury to the external sphincter.

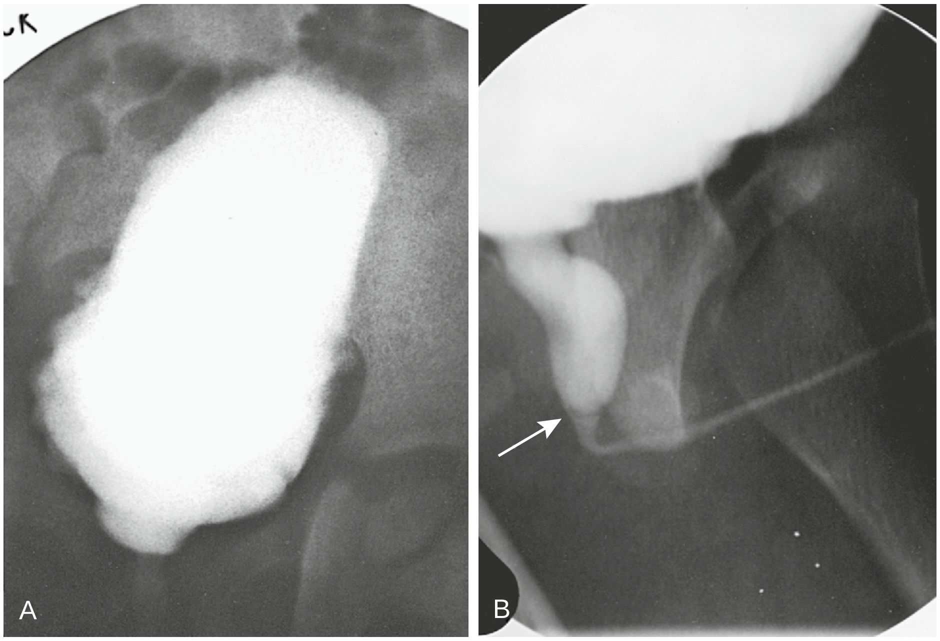

Figure 33-3 **A,** Inadequate newborn voiding cystourethrogram (VCUG).There is poor distention on the urethra and no oblique image. This was misread as a normal urethra. **B,** VCUG of a newborn with posterior urethral valves *(arrow)*. This is the same patient as **A,** but a repeat VCUG was done with adequate bladder cycling. Urethra is well dilated with voiding, revealing elongation of the prostatic urethra and bladder neck hypertrophy in the oblique image.

A Bugbee electrode passed through the working channel of a 5F cystourethroscope is a useful technique in very small infants whose urethras cannot accommodate the larger instruments. Potassium-titanyl-phosphate (KTP) laser valve ablation has been reported to be safe in newborn infants, with no urethral stricture formation at 3 years' follow-up; incontinence was not addressed in this study.[38] Because the KTP laser penetrates up to 2 mm and has some forward scatter, its use in the newborn urethra is not without risk.

On preliminary urethrocystoscopy, it is important to define the infant urethral anatomy for safe, effective treatment of the obstruction. Distortion of the normal urethral anatomy may occur secondary to obstruction and can cause confusion in distinguishing the obstructive lesion from the normal contours of the posterior urethra.

The concept of the external sphincter as a short band of circumferential striated muscle distal to the verumontanum is widely held. However, postmortem dissections in term infants demonstrate the urethral sphincter extending the entire length of the prepenile urethra.[39] The muscle is horseshoe-shaped at the bladder neck and extends down over the lateral surfaces of the prostatic urethra. The proximal extent of the sphincter can be quite prominent, causing confusion even to the experienced surgeon. Although uninterrupted from the bladder to the perineal membrane, the distal end of the sphincter as it surrounds the membranous urethra is twice as thick as the proximal end. The configuration of the sphincter changes after the newborn period, with further modifications at puberty and adulthood secondary to the muscle's association with the prostate, bulbourethral glands, and ejaculatory ducts. The verumontanum is the critical landmark to identify before valve incision. An endoscopic evaluation of congenital urethral lesions in 44 boys indicated that all obstructing lesions of the posterior urethra were attached to the caudal end of the verumontanum, extending obliquely from the back of the posterior urethra and ending distally on the anterior urethral wall.[5] The prominent distal aspect of the external urinary sphincter appears very separate from the distal end of the verumontanum and should not be confused with a valve lesion. Such a finding is common in boys with functional bladder outlet obstruction only. Once the structures are clearly identified, the valve tissue can safely be incised at the 5-, 7-, and 12-o'clock positions. An indwelling catheter is typically left in place at the end of the procedure for immediate postoperative fluid management.

Management after Valve Ablation

A common concern of pediatricians managing the patient with PUV is the persistence of severe hydroureteronephrosis after valve ablation. Frequently, this is interpreted as evidence of ureterovesical junction obstruction, and, when it is combined with elevated creatinine levels, it leads to supravesical diversion in some institutions. Chronic dilation of the collecting system and ureters from in utero obstruction or reflux does not resolve immediately but is usually not evidence of continued high intrarenal pressure. Tietjen and associates[18] used the Whitaker test to demonstrate fixed ureterovesical junction obstruction in only 4% of renal units in valve patients who had undergone proximal urinary diversion for newborn renal insufficiency. Furthermore, primary renal dysplasia was identified by biopsy in 85% of these patients. The fact that more than 40% of these patients progressed to end-stage renal failure with proximal diversion supports the belief that renal insufficiency demonstrated after newborn creatinine level stabilization is caused by underlying primary renal dysplasia and is not the result of continued obstruction.

Vigilant follow-up is essential in the neonatal period after hospital discharge. Persistent hydroureteronephrosis is common but should be closely monitored. Urodynamic evaluation can confirm that resting bladder pressures are in a safe range (<30 cm H_2O) and are not the cause of persistent hydronephrosis. Ultrasonography is also used to evaluate the renal parenchymal echogenicity and to demonstrate the presence of corticomedullary junctions. Hulbert and colleagues[40] found that distinct corticomedullary differentiation in infants with PUV imaged before 6 months of age reliably predicted serum creatinine levels lower than 0.8 mg/dL at follow-up 1 to 4 years later.

Although the obstructive effects on the prostatic urethra and bladder neck do not resolve immediately, a postoperative

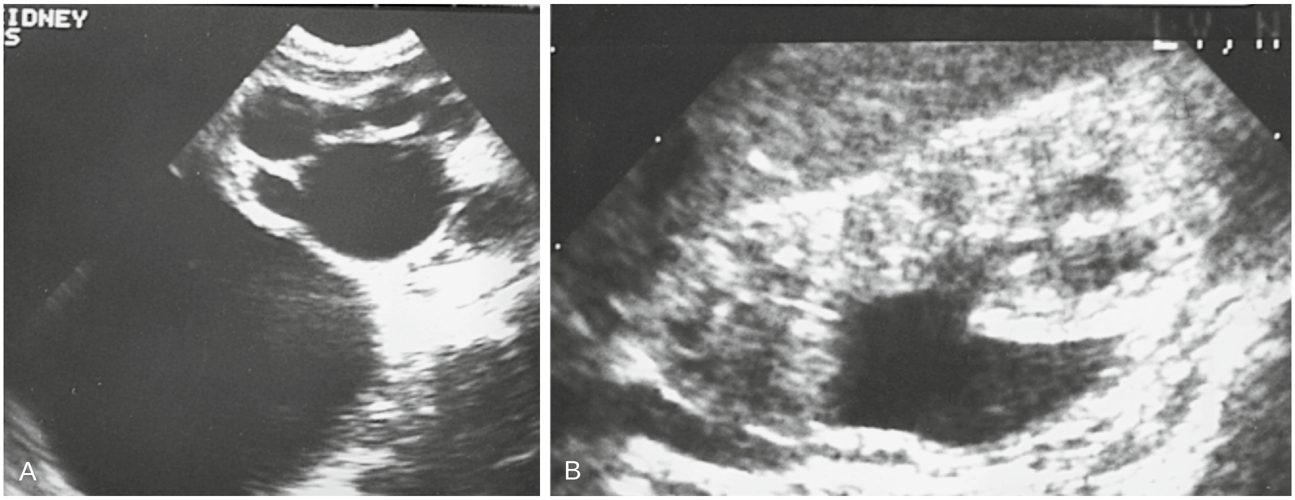

Figure 33-4 Newborn ultrasonogram in a male infant with severe renal and bladder abnormalities associated with posterior urethral valves. **A,** Left multicystic dysplastic kidney with massive right hydroureter in midline. **B,** Right dysplastic kidney.

VCUG should confirm complete valve ablation. In cases of severe preoperative urethral distortion, some surgeons prefer to perform repeat cystourethroscopy to rule out and treat possible residual valve tissue. A nuclear medicine renal scan is best obtained after 4 weeks of life to establish a baseline for differential renal function and to identify nonfunctioning renal units. Cooperative management by pediatric urology and nephrology staff facilitates the medical management in these infants. Acidosis and salt-wasting nephropathy are common and necessitate frequent monitoring of serum electrolytes.

Infants suffering the most severe degrees of obstruction typically do not survive in utero because of elective termination or fetal demise. If these infants do survive, the degree of renal dysplasia and bladder damage can be so severe that management must be tailored to allow their survival, with acceptance that both renal and bladder function are often unsalvageable.

Case Report

An infant boy was born at term with minimal maternal prenatal care and no prenatal ultrasonography. Bilateral pneumothoraces led to abdominal imaging and renal ultrasonography demonstrating bilateral cystic, dysplastic kidneys (Fig. 33-4). The VCUG demonstrated massive right VUR, several large bladder diverticula, and a small bladder (Fig. 33-5). The gross dilation of the prostatic urethra was so severe that it was initially mistaken for the bladder. The serum creatinine level fell from 4.1 to 3.9 mg/dL after catheter drainage.

Cystourethroscopy confirmed large fleshy valves, which were incised. The bladder was unusually small, and the right ureteral orifice was obscured within a large diverticulum. At 6 weeks of life, a furosemide (Lasix) renogram was obtained that demonstrated no function in the left kidney and poor drainage from the right refluxing kidney. Ultrasonography continued to demonstrate poor right renal parenchyma, right hydroureteronephrosis, and a left cystic kidney without visualization of the left ureter. In the first 4 months of life, the infant developed recurrent episodes of urosepsis despite prophylactic antibiotic therapy. A right end-cutaneous ureterostomy was performed, at which time a narrowed ureteral segment proximal to the right paraureteral diverticulum was found. After diversion, the infant had no further episodes of infection. The patient required dialysis beginning at 8 months of age. The diverted bladder capacity at 2 years of age was 5 mL, and a sigmoid conduit was created before renal transplantation.

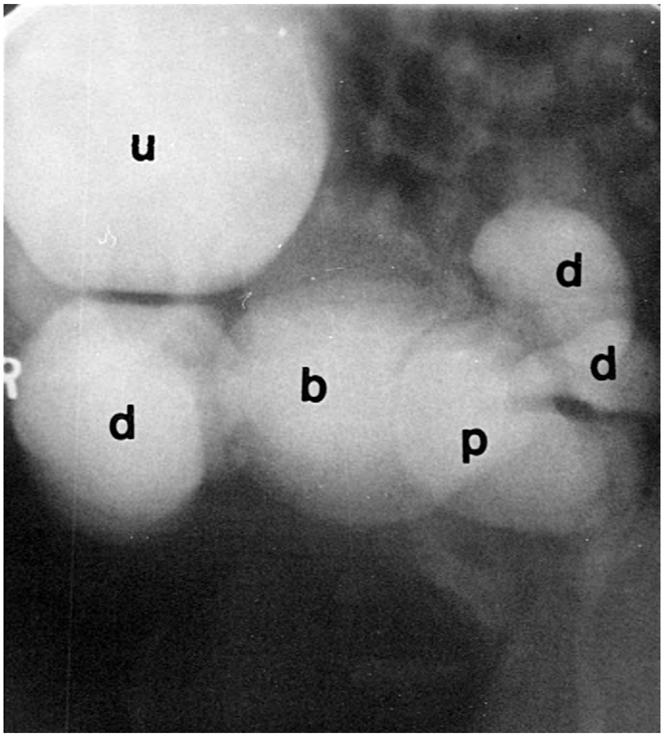

Figure 33-5 Newborn voiding cystourethrogram in a patient with severe urethral obstruction (same infant as in Fig. 33-4). Note the small bladder (b) with multiple diverticula (d) and high-grade right vesicoureteral reflux into the grossly dilated right ureter. p, prostatic urethra; u, right refluxing, obstructed ureter.

This case demonstrates the extreme example of both renal and bladder impairment associated with PUV. Fortunately, most infants have reasonable preservation of bladder and kidney function and do well with careful management.

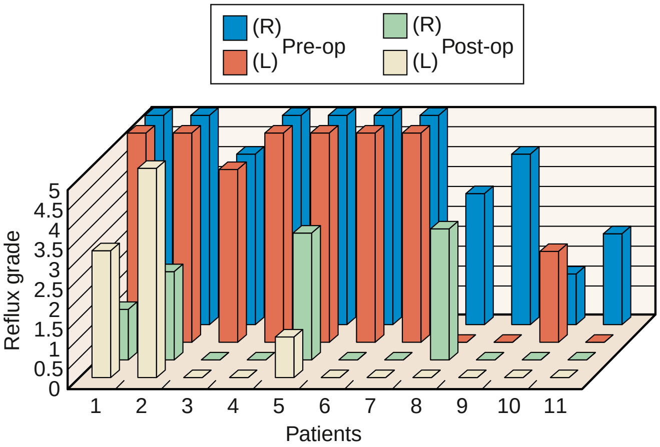

Figure 33-6 Spontaneous resolution of vesicoureteral reflux 1 year after valve ablation alone. Results from 19 refluxing units in 11 patients are depicted. Persistence of reflux is associated with a nonfunctioning renal unit in 2 patients and upper tract duplication in 1 patient. Post-op, 1 year postoperative; Pre-op, before valve ablation; L, left; R, right.

Table 33-1 Anatomic Changes and Clinical Consequences in the Valve Bladder Syndrome

Organ	Pathology	Clinical Results
Kidneys	Dysplasia, concentrating defect	High urine volume
Ureters	Dilated, poor peristalsis	Large "dead space" Poor emptying Possible obstruction after reimplantation
Bladder	Poor compliance, relatively small volume, reduced sensation to high pressure	High bladder pressure most of time Progressive renal damage Progressive bladder damage
Urethra	Voiding dysfunction	Difficulty with bladder emptying Magnified bladder pressure effect

VESICOURETERAL REFLUX RESOLUTION AFTER PRIMARY VALVE ABLATION

VUR occurs in up to 75% of infants diagnosed with PUV in the first year of life.[21,41] Traditionally, routine management of these patients has included ureteral reimplantation, often done at the same time as contralateral nephroureterectomy of nonfunctioning renal units. There is long-standing evidence that reimplantation is not necessary in most valve patients, and conservative management alone is safe and effective.[41] In a series of infants treated by primary valve ablation alone, Close and coworkers[21] found improvement in reflux grade in 18 of 19 refluxing renal units after 1 year (Fig. 33-6). Complete resolution of reflux occurred within 2 years after valve ablation in 12 (86%) of 14 patients. Reflux into nonfunctioning kidneys typically does not resolve.[27] Nephroureterectomy has been performed in the past to improve voiding dynamics in these patients, although ureteral preservation for possible ureterocystoplasty is appropriate in some cases.[42-44]

BLADDER FUNCTION IN VALVE PATIENTS

There is wide acceptance of the concept that maximizing the long-term outcome in PUV patients centers on maintaining bladder function. Older patients with a missed diagnosis of severe PUV and valve patients with a history of urinary diversion were described by Mitchell in 1986[45] as illustrative cases of the "valve bladder syndrome." For many, recognition of this syndrome has changed the approach to management of PUV in infants.

Boys with a valve bladder demonstrate the long-term effect of persistent renal obstruction from high bladder pressures after relief of urethral obstruction. Pathologic changes in the entire urinary tract combine to further compromise renal function (Table 33-1). Progressive hydroureteronephrosis, polydipsia, polyuria, urinary frequency, and enuresis with renal insufficiency are hallmarks of the syndrome. Renal tubular dysfunction results in a severe urine concentrating defect with polyuria and polydipsia. Urine production in these children can range from 3 to 6 L/day. In patients with VUR and grossly dilated upper tracts, ureteral peristalsis is poor, and large urine volumes result in incomplete emptying of the collecting system, ureters, and bladder. The thick-walled valve bladder is poorly compliant and functionally lacks normal sensation. These patients learn to tolerate high intravesical pressures and are able to hold large urine volumes at these pressures without pain. With gross distention, the thick wall of the bladder causes increased resistance to urine flow through the ureterovesical junction. Urine holding thus results in increased upper tract dilation and pressure and, ultimately, causes progressive renal damage.

There is an increasing focus on the role of the bladder in the long-term outcome of patients with PUV. Urodynamic patterns described in older valve patients include bladder hyperreflexia, hypertonia (noncompliance), and myogenic failure.[46] Although these changes are attributed to bladder outlet obstruction, the contribution of primary treatment to dysfunction cannot be ascertained from such reports. Many of the studies of bladder and ureteral function in valve patients are complicated by the inclusion of different primary treatment modalities and treatment ages in the same study group.

Studies have now been published that focus on the functional outcome in newborns undergoing primary ablation alone for the treatment of congenital urethral obstruction. Holmdahl and associates[47] demonstrated normal bladder compliance by 1 year of age in all infants undergoing primary valve ablation at a mean age of less than 2 months. They did not find the three dysfunctional patterns described by Peters and colleagues[46] in older boys. In a retrospective evaluation of 23 newborn infants treated by valve ablation in the first weeks and followed up from 1 to 9 years, Close and coworkers[21] found good bladder function as well as resolution of upper tract abnormalities. VCUG performed 1 year after valve resection showed resolution of trabeculation in more than 85% of patients (Fig. 33-7).Additionally, when compared with infants treated by urinary diversion, those boys undergoing early valve ablation had significantly better bladder compliance and potty-training results. The mean bladder compliance was 17.2 mL/cm H_2O in those infants treated by early primary incision, compared with 5.8 mL/cm H_2O in boys treated by diversion. Ninety-two percent of the boys undergoing early ablation were potty trained by 4 years of age, whereas only 17% of the diverted boys were dry by age 4. Low bladder compliance and high bladder pressures led to bladder augmentation in 3 (38%) of the 8 diverted

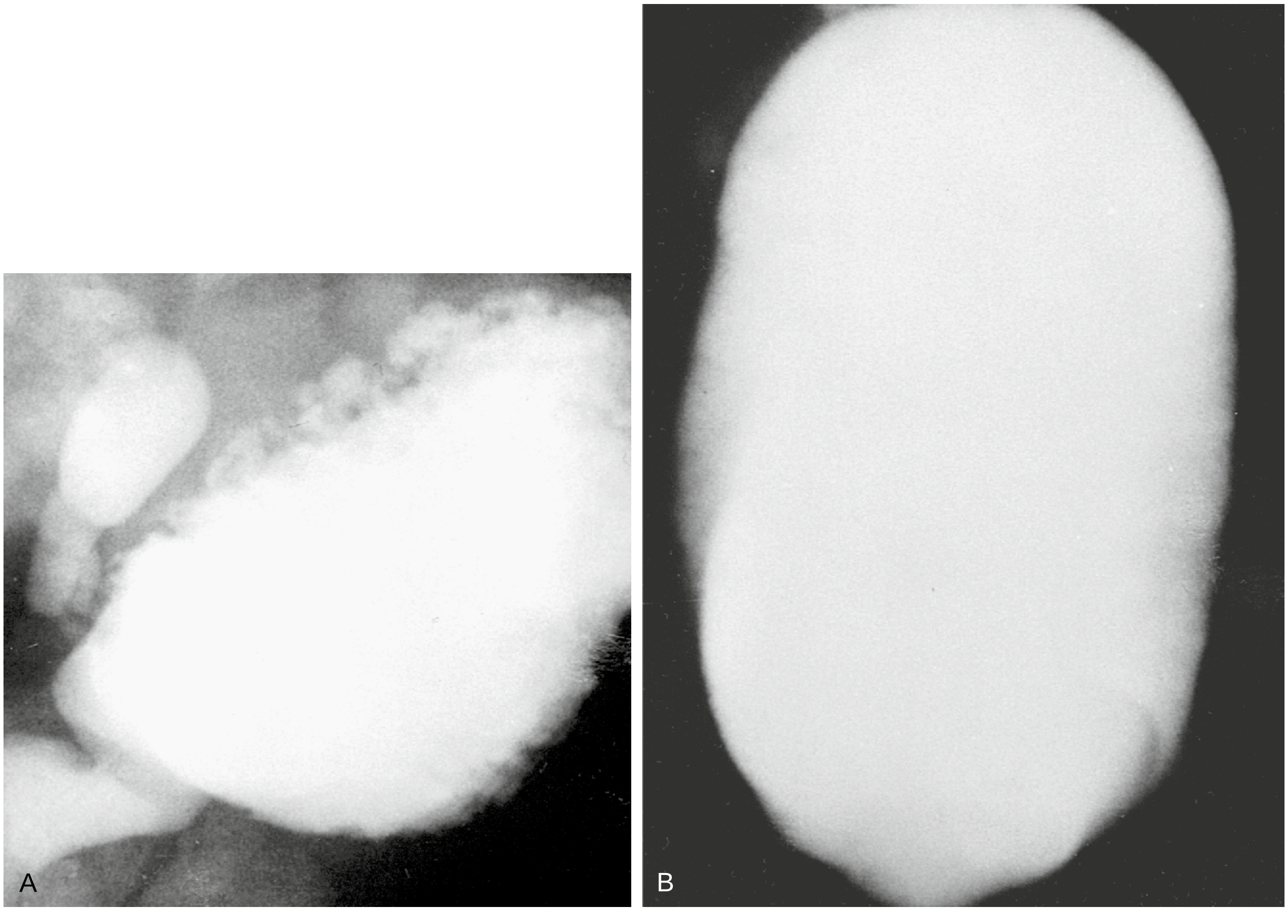

Figure 33-7 **A,** Voiding cystourethrogram (VCUG) of a newborn infant with posterior urethral valves. Note bladder wall trabeculation and diverticula. **B,** VCUG of the same patient 1 year after newborn valve ablation demonstrates a healed bladder with a smooth wall and normal capacity.

patients. Only 1 (4%) of 23 patients undergoing primary ablation required bladder augmentation, and that patient had severe urethral obstruction that was undetected until 4 months of age.

URETHRAL VALVES AND RENAL TRANSPLANTATION

Chronic renal failure necessitates renal transplantation in a significant number of boys with PUV. With appropriate management, many patients with moderate renal insufficiency at birth reach adolescence before requiring transplantation. Modern studies have addressed the possible detrimental effects of the valve bladder on renal graft survival.

Reinberg and colleagues[48] demonstrated significantly poorer 5-year graft survival for patients undergoing transplantation for valve-related renal failure than was found in those patients with nonobstructive etiologies. Similarly, Dewan and associates[49] reported that valve bladder led to allograft failure in 12% of valve patients receiving a renal transplant. Other authors[50,51] have demonstrated good allograft survival but elevated creatinine levels occurring over long-term follow-up in transplanted valve patients.

A large study with 10-year follow-up after renal transplantation demonstrated no difference in graft survival and creatinine levels when comparing children with PUV and children with nonobstructive causes of renal failure.[52] These data may reflect the improvement in urologic management of valve bladder. The conclusion that the valve bladder will not negatively affect renal allografts is not supported by a long-term follow-up evaluation addressing bladder function and outcomes of renal transplantation. Salomon and coworkers[53] reviewed the voiding history of 44 valve patients who were monitored for a mean of 9 years after renal transplantation. They found an elevation of serum creatinine after 5 years of follow-up in boys with symptoms of bladder dysfunction including incontinence, urinary urgency, frequency, and difficulty emptying. Because of the relentless effects of the bladder on the upper tracts, the preservation of bladder function must be of primary consideration in all patients with PUV as management decisions are made.

REFERENCES

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CHAPTER 34

URETHRAL DUPLICATION AND OTHER URETHRAL ANOMALIES

Guy A. Bogaert

DEVELOPMENT AND ANATOMY

The female and male urethra have clearly different developmental paths and anatomy. Early in development, at about 3 to 6 weeks of gestation, the components of the musculature of the bladder neck, trigonal system, and ventral urethral wall are identical in female and male fetuses. At the end of the 6th week of gestation, the urogenital membrane retracts and the phase of sexual differentiation begins. The Leydig cells of the fetal testes become hormonally active and induce a significantly higher testosterone level between the 8th and the 20th weeks of gestation. After this period, the testosterone level is identical in female and male fetuses.[1]

Development and Anatomy of the Female Urethra

The female urethra derives from the endoderm of the urogenital sinus. During fetal development, the posterior ends of the urethral folds fuse, and the remaining portion develops into the labia minora. The proximal smooth muscle part of the female urethra inserts into the extension of the superficial trigone and surrounds the ventral part of the urethra. The distal part inserts more dorsally in a way similar to that in the dorsal part of the male membranous urethra.

The striated urethral muscle has two parts, one around the urethra itself and one around the urogenital sinus. The muscle is continuous throughout the complete urethra. The caudal part of the muscle that lies below the pelvic floor will become attached laterally to the ischiopubic bone (Fig. 34-1).[1]

The length of the urethra at birth is less than 1 cm, and in the adult it is 4 cm. The internal diameter during micturition averages between 0.1 and 0.4 cm. However, the internal urethra can be normally stretched up to a Charrière number equal to the age in years plus 10 (during urethral calibration).[2] The urethral mucosa is composed of pseudostratified columnar epithelium, with more transitional epithelium near the bladder and stratified squamous epithelium near the external meatus.[3]

Development and Anatomy of the Male Urethra

The formation of the male urethral plate and growth of the genital tubercle coincide during fetal development. It is during the 8th week of gestation that the genital tubercle grows over the urogenital membrane. As the phallus enlarges, its floor is formed by the urogenital membrane. The urethral plate is formed at the same time from a strip of sagittally staked endodermal cells that move into the mesodermal core of the genital tubercle.[4] Later, the urethral plate extends further within the mesenchyma of the phallus, and its partial degeneration forms the secondary urethral groove (Fig. 34-2).[1]

A different mechanism occurs in the development of the glandular segment of the urethra. A plug of ectoderm from the tip of the glans invades the mesenchyme, and, as it invades more deeply, it develops a lumen at the same time that the urethral folds enclose more of the urethral plate. The plug of ectoderm correlates with the anatomic fossa navicularis (Fig. 34-3).

The normally developed urethra consists of the prostatic urethra (region 1), the bulbomembranous urethra (region 2), the bulbospongious urethra (region 3), and the penile or pendulous urethra (region 4) (Fig. 34-4). The bulbomembranous urethra consists of the striated urethral sphincter and lies in the urogenital diaphragm. The bulbospongious urethra consists of the suspensory ligament, and the bulbourethral Cowper ducts typically end in this segment of the urethra. The penile or pendulous urethra is characterized by the fact that it extends from the suspensory ligament to the external meatus. It is typically surrounded by the corpus spongiosum, which functions only during sexual activity.

PATHOLOGIC CONDITIONS

Timing of the Urethral Anomalies

1. Urethral duplication: 10 to 14 weeks of gestation
2. Anterior urethral valves–urethral diverticulum: various prenatal
3. Syringocele: various prenatal
4. Urethral prolapse: various postnatal
5. Urethral stricture: various postnatal
6. Urethrorrhagia idiopathica posterior: puberty
7. Cowper duct and cysts: 10 to 14 weeks of gestation to postnatal

Duplication of the Urethra

Urethral duplication is a rare congenital anomaly that has been known for a very long time. The earliest descriptions go back to Aristotle and Vesalius.[5-7] Since then, duplication of the urethra has been reported several times in case reports or small series.[8] Urethral duplication is reported mainly in young children, although it is sometimes discovered in adulthood.[9]

Classification

The anatomic diversity and lack of a uniform embryologic theory have led to many classifications of urethral duplication. As a consequence, there is a confusion in the literature concerning complete versus incomplete duplication and accessory urethra versus urethral duplication.

According to Ortolano and Nasrallah,[6] a *urethral duplication* must originate from the bladder, bladder neck, or prostatic urethra. An *accessory urethra* originates distally off the prostatic urethra or is a blind-ending passage rising from a separate external opening.

Middleton and Melzer[7] considered a *complete urethral duplication* to originate proximally from the external urethral sphincter, whereas an *incomplete urethral duplication* originates distally from that sphincter. They also recognized two channels ending in one external orifice as an internal urethral duplication. In Table 34-1, a more clinical classification elaborated by Williams and Kenawi is outlined.[10] This classification is simple and was reported frequently in the literature.[11,12]

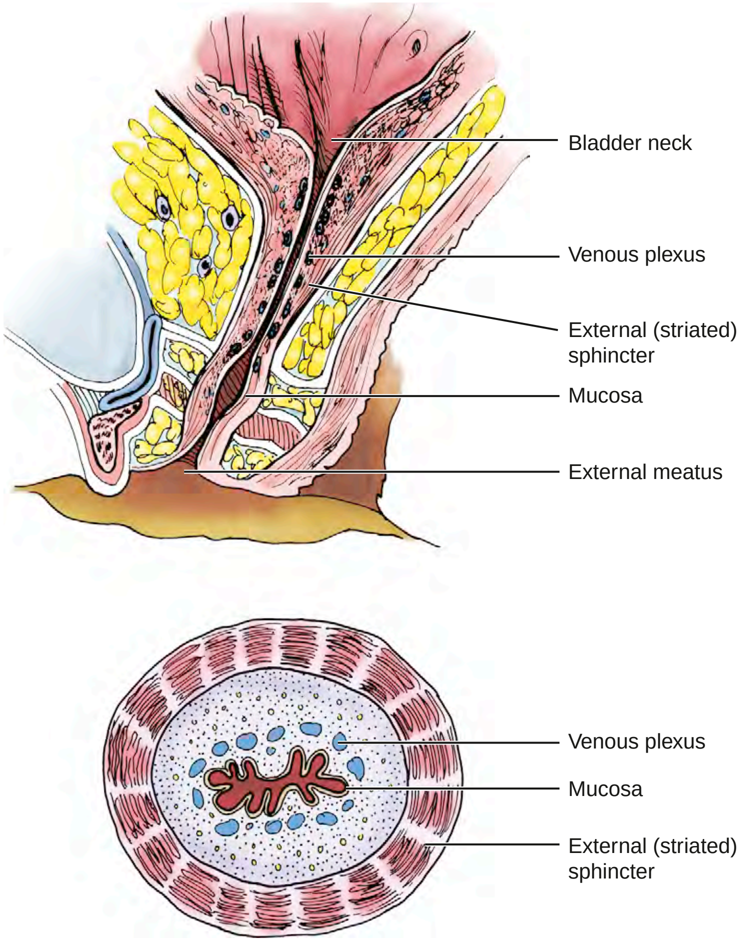


Figure 34-1 The female urethral mucosa is composed of pseudostratified columnar epithelium. Toward the bladder, the epithelium is more transitional and merges with the lining of the bladder neck. Under the mucosa is an important layer of venous plexus, and this is circumferentially surrounded by the external striated sphincter.

It makes a distinction between duplications in the sagittal plane (in which the duplicated urethra passes above or below the normal urethra) and collateral duplications (in which the two urethras are lying side by side). Sagittal duplications occur only in the male; collateral duplications are rarer and occur in both the male and the female. Moreover, collateral urethral duplications often form a part of a partial or complete caudal duplication syndrome.

However, we recommend a more complete classification, as proposed by Effmann and associates (Fig. 34-5).[13] This classification is mostly currently reported in the literature (Table 34-2).[14-17]

Almost all blind-ending urethral duplications belong to the distal *type IA* (see Fig. 34-5A). The exact incidence is unknown, because this situation is mostly clinically irrelevant and asymptomatic. The accessory urethra is usually situated dorsal to the functional urethra, regardless of its normal or ectopic position (Fig. 34-6). Similarly, a blind-ending sinus is found in many hypospadias patients and can be explained by the embryologic development. This supplementary opening should always be catheterized, to exclude a complete duplication. A blind accessory urethra does not usually cause any symptoms, although a purulent excretion can occur.

Very rare are the urethral duplications of *type IB* (see Fig. 34-5B), in which a blind-ending channel rises from the urethra (dorsally) and does not reach the skin. These cases are very difficult to differentiate from narrow-mouthed urethral diverticula or dilated Cowper ducts (ventrally). Clinically, leakage after micturition is the most frequent symptom.

If the urethral duplication is complete, it can be divided into three types. The most common type is the duplication in which two noncommunicating urethras originate from the bladder with the meatus of the dorsal urethra in epispadiac position *type IIA1* (Fig. 34-7; see Fig. 34-5C). The ventral urethra is situated in an orthotopic position and is the more functional one. The epispadiac opening can be located anywhere on the dorsum of the penis, from the base of the penis to the glans (see Fig. 34-7A).

Less common is the situation in which two urethras arise from the bladder but the dorsal urethra is orthotopic and the ventral urethra opens in hypospadiac position, anywhere from the penoscrotal junction up to the glans. In this situation, the ventral urethra is the more functional one, and the dorsal urethra is usually atretic.

A different and the least common situation is the collateral urethral duplication without duplication of the bladder, in which both urethra and meatus are located side by side (frontal duplication). In this situation, both urethras are equal in function.

In *type IIA2*, the urethra bifurcates distal to the bladder, usually at the height of the prostatic urethra and with the most functional urethra in hypospadiac position (sagittal duplication) (see Fig. 34-5D). This situation is somewhat similar to type IIA1 and is often called *incomplete urethral duplication*. This term is misleading, however, because it can be confused with a blind accessory urethra. A special subtype of the type IIA duplication is a Y-shaped urethral duplication in which the ventral canal opens toward the

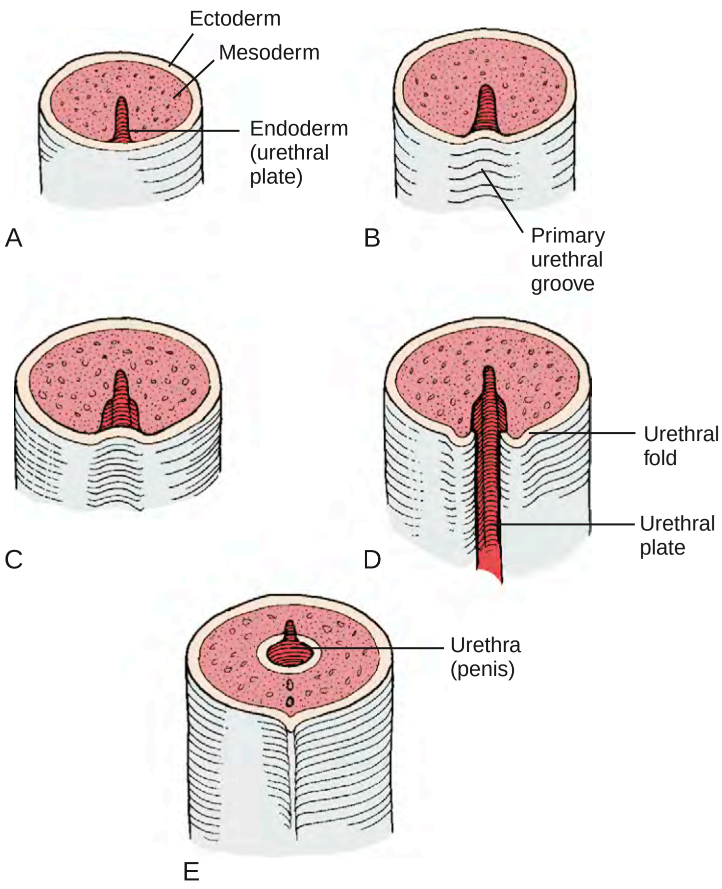


Figure 34-2 Transverse sections show the formation and closure of the male urethral groove. (Adapted from Hinman F Jr. *Atlas of Urosurgical Anatomy.* Philadelphia: WB Saunders; 1993: 421, 422).

perineum, the anal mucocutaneous transition, or the anal canal (see Fig. 34-5E). It is referred as Y-duplication, congenital urethroperineal fistula, or congenital H-type urethroanal fistula (Fig. 34-8).

Type IIB is a very rare situation of urethral duplication in which the urethra initially bifurcates and then fuses again. It is sometimes referred to as *spindle urethra* (see Fig. 34-5F).

A final type of urethral duplication, *type III*, involves not only a duplication of the urethra but also a duplication of the bladder or phallus (frontal duplication). This refers to complete collateral duplications. Bladder duplication with or without urethral duplication occurs more often in females, but it can also be found in the male.[11] In most cases, associated congenital anomalies of the gastrointestinal tract and the rest of the lower genitourinary tract, as well as vertebral and renal anomalies, are present.

Embryology

The embryologic explanation of urethral duplication remains unknown. However, various theories have been proposed. One theory considers that the defect arises in the 7th week of embryologic development, when the urorectal septum, which consists of a superior mesodermal fold (fold of Tourneux) and two lateral mesodermal folds (folds of Rathke), divides the cloaca into a posterior rectum and an anterior primitive urogenital sinus.[18] Another theory states that if the urorectal septum does not cease to grow, it can split not only the cloaca but also the onset of the urethra.[7] A third theory hypothesizes that the ingrowth of the mesonephric wolffian duct leads to division of the primitive urogenital sinus into a superior urethrovesical channel and an inferior definitive urogenital sinus.[19]

It is known that, in the 6th week of embryologic development, the definitive urogenital sinus forms a urethral groove on the genital tuberculum, which is a median mesodermal swelling anterior to the urogenital membrane. This groove is filled up with a solid endodermal urethral plate, but it is not known whether the plate resorbs or ruptures to later form a part of the urethra (see Fig. 34-2). A supplementary urethra could be formed if the urogenital plate persisted and canalized all along the penis.[5,6] In the 5th week, the cloacal folds are formed lateral to the cloacal membrane; after fusion of the urorectal septum with the cloacal membrane, these are called the *urogenital folds*. The urogenital folds fuse in the midline after the 12th week, forming the penile urethra and the median raphe.[19] It is considered that a defect in the fusion of the urogenital folds is responsible for the origin of an ectodermal and an endodermal urethral channel.[5,6]

However, Woodhouse and Williams[11] stated that one theory explaining all urethral duplications seems unlikely. It is indeed most unlikely that bladder duplication with collateral urethral duplication would be caused by the same embryologic defect as that leading to the sagittal urethral duplications. As with other midline structures originating from the fusion of lateral elements, each lateral element is able to form the complete organ if no fusion of the lateral elements occurs.[10] This could explain bladder duplication with collateral urethral duplication that occurs without the situation of a functional and atretic urethra (as in the sagittal situation).

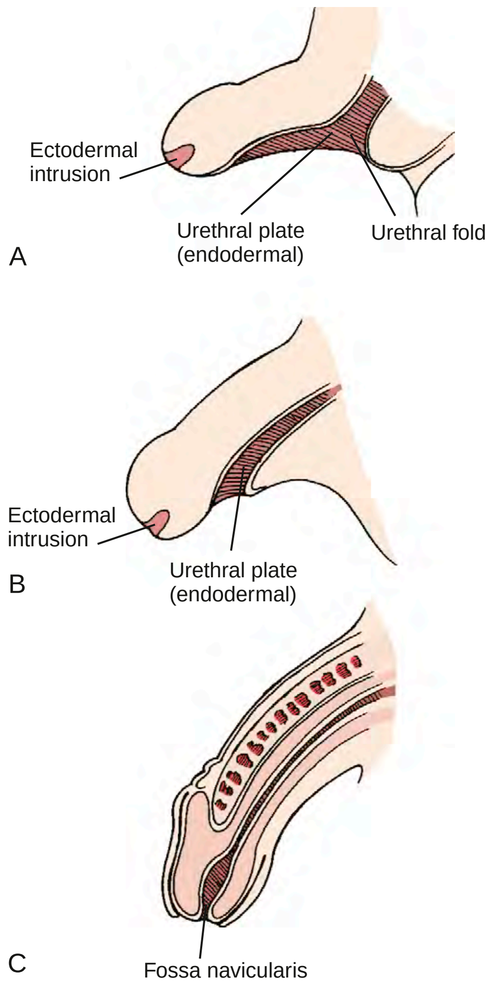


Figure 34-3 Longitudinal sections show the development of the glandular region and fossa navicularis of the male urethra. (Adapted from Hinman F Jr. *Atlas of Urosurgical Anatomy.* Philadelphia: WB Saunders; 1993:422.)

Associated Findings

Patients with a urethral duplication and an epispadiac meatus frequently have a wider symphysis pubis, as is found in patients with isolated epispadias or exstrophy (see Fig. 34-7D). As mentioned previously, the infraumbilical wall, the genital tubercle, and the symphysis pubis are formed by the ingrowth of lateral mesoderm between the ectodermal and the endodermal layers of the cloacal membrane.[10] If the cloacal membrane ruptures too early or is too long and splits the genital tubercle, the mesodermal structures are not capable of closing the midline defect.[18] In the case of isolated epispadias, the cavity on the dorsum of the penis (former genital tubercle) is linked with the definitive urogenital sinus. If, however, the urethral plate canalizes all along the penis, urethral duplication with an epispadiac opening could arise. The abnormally wide symphysis pubis in these patients strongly suggests that this type of urethral duplication originates according to the same embryologic mechanism as the epispadias-exstrophy complex.[10,13]

A type IIA2 urethral duplication with a Y-shaped urethra might be caused by a failure in the alignment of the folds of Tourneux and Rathke, so that a congenital urethroperineal fistula is formed.[13] However, the urethroperineal or urethroanal urethra is the more functional one, and the orthotopic urethra is atretic, so a defect in the anterior urogenital sinus during the first half of pregnancy might be the cause of this problem in the anterior urethra. In this stage of embryologic development, the cells lining the fistula toward the perineum or anus would still have enough potential to form a functional urethra.

Clinical Findings

Symptoms vary and are dependent on the type of urethral duplication. Each form of duplication can be completely asymptomatic. The blind accessory urethra (type IA; see Fig. 34-6), in particular, causes little inconvenience, except for occasional mucus and purulent excretion coming from an infected accessory channel. This is an indication for surgical excision. A hypospadiac accessory urethra, type IIA2, also rarely causes any symptoms, but it should be explored radiologically if it is uncertain whether the channel ends blindly.[9]

If the duplication is complete (type IIA1; see Figs. 34-5C and 34-7A), the most common symptoms are double urinary stream, recurrent urinary infections, outflow obstruction, and sometimes incontinence. This kind of duplication is often associated with chordae that cause a dorsal curvature of the penis in erection. Again, this reminds one of the clinical features seen in patients with isolated epispadias. Stress incontinence can occur but is seen invariably. The reason for this phenomenon is the fact that the secondary urethra is not "normally" surrounded by the urethral sphincter mechanism.

Complete duplications with hypospadiac meatus (the most common of the type IIA2 anomalies; see Fig. 34-5D) often cause outflow obstruction. As always, the dorsal orthotopic urethra is atretic, and the ventral hypospadiac urethra is the more functional one. Outflow obstruction is caused by a mucus plug in the orthotopic urethra or by proximal dilation of the dorsal urethra that compresses the ventral urethra during micturition.[9]

A spindle urethra, type IIB (see Fig. 34-5F), can also cause outflow obstruction symptoms. It is caused by the turbulences during voiding, and it might even affect the upper urinary tract (hydroureteronephrosis, bladder trabeculation) or cause overflow incontinence.

Type IIA2 urethral duplications with a Y-shaped urethra cause perineal or anal urinary leakage. The more ventral urethra (i.e., the urethroperineal channel) is usually the more functional one and consequently needs to be spared in case of surgical correction. However, in this group of patients, exceptions to the rule that the dorsal urethra is atretic can occur. In a small group of Y-shaped urethral duplications, a normal dorsal urethra and a hypoplastic urethroperineal canal can be found (see Fig. 34-8). In these patients, it is the ventral hypoplastic urethra that can be removed surgically.[13] Bates and Lebowitz[16] even proposed to consider this not a duplication but a separate entity, a *congenital urethroperineal fistula*. However, it should remain within the group of urethral duplications, because the "fistula" has histopathologically all characteristics of a normal urethra, and no typical predestining factors toward fistula formation (i.e., infection, trauma, strange body) can be found.[17] In view of treatment, it is very important to make a distinction between a real Y-shaped urethral duplication (type IIA2) and a so-called congenital urethroperineal fistula. The clinical symptoms are different: in the case of a Y-shaped duplication, most of the urine passes through the urethroperineal channel, whereas in the case of a congenital urethroperineal fistula, there is a normal urinary stream coming from the orthotopic urethra with only some perineal wetting. Therefore, patients with congenital urethroperineal fistula are seen at a later age. In addition, the more functional urethra can be determined by radiologic examination during a voiding cystourethrogram (VCUG; see Fig. 34-8).

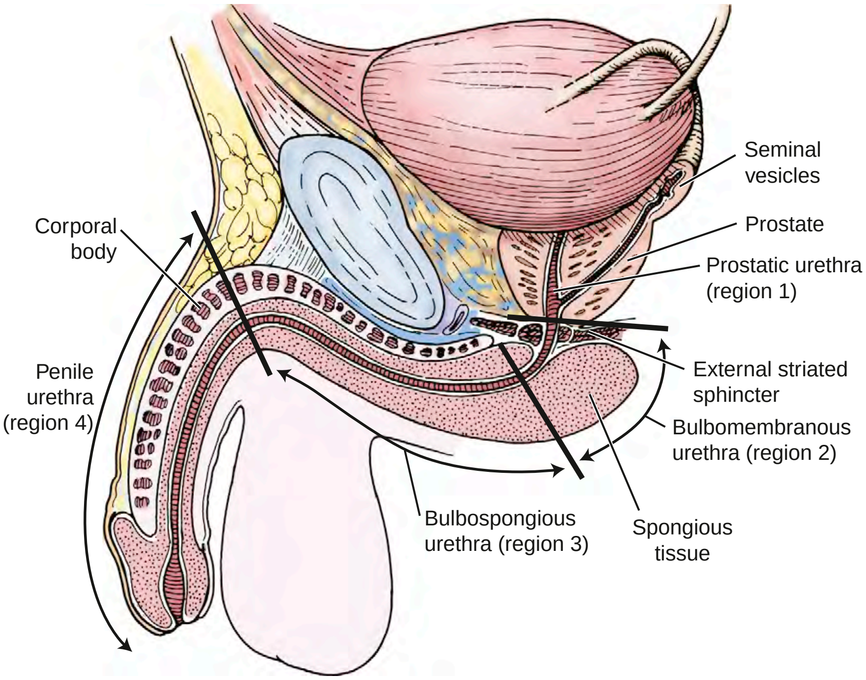

Seminal vesicles
Prostate
Prostatic urethra (region 1)
Corporal body
External striated sphincter
Penile urethra (region 4)
Bulbomembranous urethra (region 2)
Bulbospongious urethra (region 3)
Spongious tissue

Figure 34-4 Schematic structure of the male urethra: prostatic urethra, bulbomembranous urethra, bulbospongious urethra, and the pars pendulans or penile urethra.

Table 34-1 Urethral Duplications: Classification of Williams and Kenawi

Sagittal Duplications

Epispadiac (dorsal penile accessory meatus)

- Complete: two channels leave the bladder separately
- Incomplete: one channel from the bladder divides distally
- Abortive: blind penile sinus

Hypospadiac (both urethras beneath corpora cavernosa)

- Complete: two channels leave the bladder separately
- Incomplete: urethra divides below the bladder
- Abortive: both orifices in hypospadiac position, with the blind sinus lying dorsal to the urethra

Spindle urethra (the urethra splits into two and then reunites)

Y duplication (perianal or perineal accessory channel)

Collateral (Frontal) Duplications

Complete with diphallus

Abortive, one urethra being impermeable

Data from Williams DI, Kenawi MM. Urethral duplications in the male. *Eur Urol.* 1975;1:209-215.

If a collateral urethral duplication or a true Y-shaped urethral duplication (type IIA2) is found, a complete workup with investigation of the spine, kidneys, and lower genitourinary and gastrointestinal tracts should be performed.

Diagnosis

If clinical suspicion of urethral duplication exists, besides the physical examination, a complete visualization of both channels should be sought. An antegrade VCUR should be performed. If there is incomplete visualization of both channels, retrograde urethrography can sometimes demonstrate their pattern more precisely.

Urethrocystoscopy and simultaneous catheterization of the second channel with a guidewire can be useful to accurately establish the proximal opening (see Fig. 34-7C). With a Y-duplication, it is sometimes difficult to delineate the distal opening as being perineal or perianal. Injection of methylene blue into the normal urethra or after suprapubic injection can be helpful.

In general, these patients do not have associated upper tract abnormalities, and a renal ultrasonogram is part of the routine workup.

A radiologic assessment of an abnormally wide symphysis orients the diagnosis toward complete or incomplete urethral duplication with an epispadiac supplementary opening.

Treatment

The treatment should be adapted to the individual patient and should be focused on the possible problems such as urinary tract infections, infertility, and deviation during erection. If fertility is a problem or should be preserved, one should be aware that the ejaculation will occur via the most functional channel.

Patients with a type IA or IB urethral duplication rarely have clinical symptoms. However, if infection and purulent secretions occur, excision of the secondary channel (type IA) or endoscopic excision (type IB) is advised.

Patients with a type IIA1 complete urethral duplication can present with recurrent urinary tract infections and possibly with significant dorsal penile curvature. If the patient has only urinary tract infection and some dribbling, fulguration of the duplicated channel can be performed, but because of recanalization or postoperative fibrosis with consequent curvature of the penis, this should not be the first choice of treatment.[17] In addition, if a dorsal penile curvature exists initially, it is recommended to excise the dorsal accessory urethra, beginning with a circumferential glandular incision and dissecting the accessory urethra toward the symphysis. The proximal part

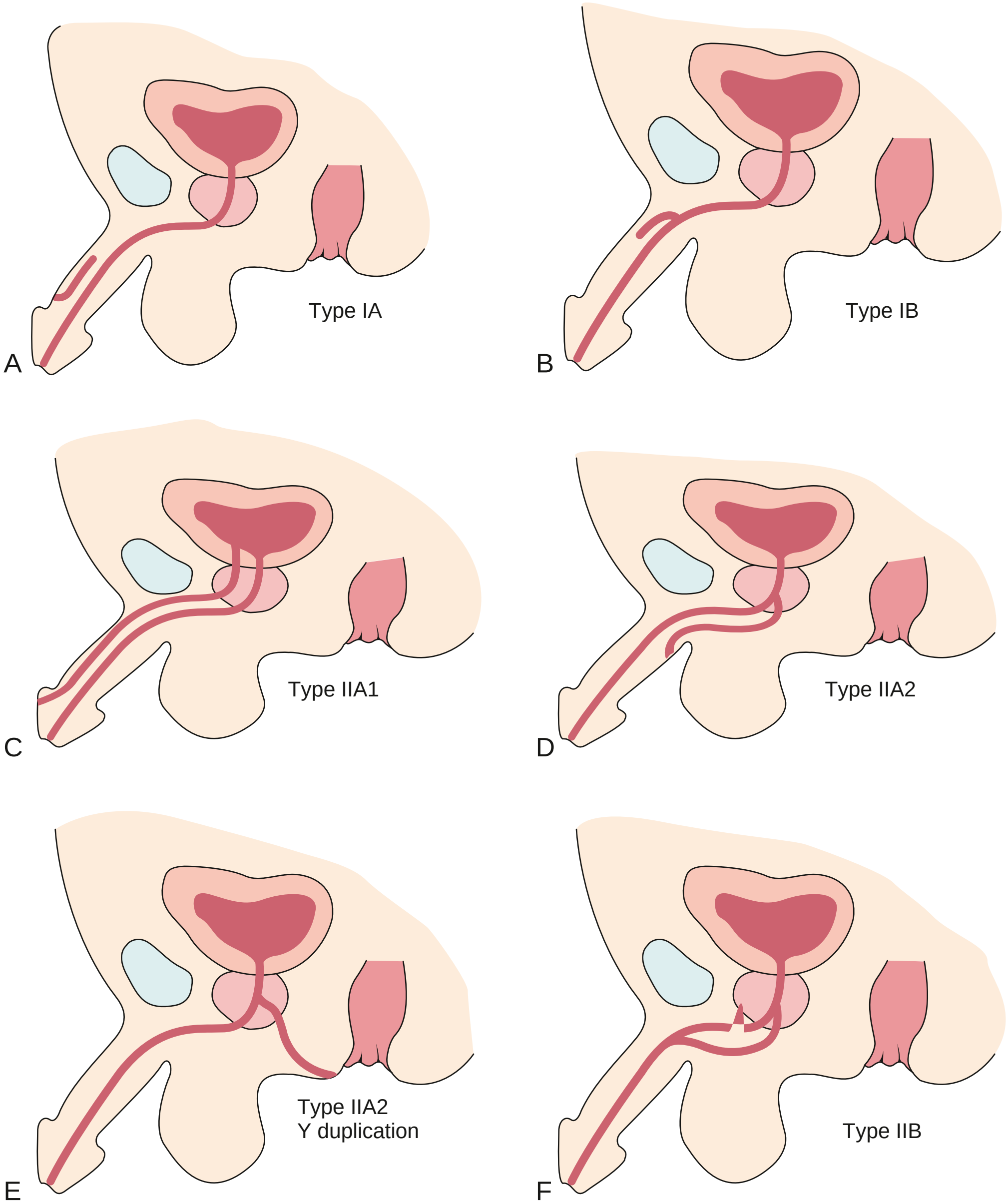


Figure 34-5 The classification of urethral duplication developed by Effmann and associates.[13] **A,** Type IA: distal blind duplication. **B,** Type IB: proximal blind duplication. **C,** Type IIA1: two noncommunicating urethras. **D,** Type IIA2: urethra bifurcates distal of the bladder. **E,** Type IIA2 with Y-shaped duplication. **F,** Type IIB: urethra bifurcates and re-fuses. (Courtesy of Jochen Darras, M.D.)

of the dorsal urethra or channel runs under the usually wide intersymphyseal ligaments. If the symphysis is not separated as usual, a suprapubic abdominal approach may be necessary. At the point of proximal dissection, care must be taken to remain in the midline plane and not to injure the cavernosal nerves, which enter the corporal bodies laterally. If, after excision of the dorsal urethra, the dorsal curvature persists, plication of the corporal bodies at the ventral side or corporal rotation (ventrally) should be performed.

Special attention should be given to patients with an accessory "hypospadiac" urethra that might be a Y-duplication (type IIA2) or a genuine type IIA2 anomaly. Excision of the wrong channel can result in incontinence or urinary retention. In a patient with a dorsal hypoplastic urethra, this orthotopic but hypoplastic urethra must be removed, after which a classic hypospadias correction can be performed. However, if the distal end of the dorsal atretic urethra has a normal caliber, a urethroplasty anastomosing the ventral urethra with the dorsal urethra might be a good alternative.[6,7]

If the patient appears to have a hypoplastic urethroperineal canal with orthotopic normal functional urethra, the urethroperineal canal can be removed through a perineal incision.

For some urethral duplications in which the two channels are running beside each other, some authors suggest a transurethral incision of the interurethral septum.[11,12] This technique is useful for patients with a spindle urethra and collateral urethral duplication, but it appears to be less successful for those with other urethral duplications.[6,7]

Anterior Urethral Valves and Urethral Diverticulum

Anterior valves are not common; they are 10 times less frequent than posterior urethral valves.[20] Because of the location distal of the urethral sphincter, anterior valves are often

Table 34-2 Urethral Duplications: Classification of Effmann, Lebowitz, and Colodny

Type I: Blind, incomplete urethral duplication or accessory urethra
  - IA—Distal: opens on the dorsal or ventral surface of the penis but does not communicate with the urethra of bladder
  - IB—Proximal: blind-ending channel arising from the urethra

Type II: Complete patent urethral duplication
  - IIA—Two meati
    - IIA1—Two noncommunicating urethras independently arising from the bladder
    - IIA2—Second channel arises from the first and courses independently into a second meatus
  - IIB—One meatus
    - IIB1—The urethra splits into two and then reunites

Type III: Urethral duplication as a component of partial or complete caudal duplication

Data from Effmann EL, Lebowitz RL, Colodny AH. Duplication of the urethra. *Radiology.*1976;119:179-185.

associated with a urethral diverticulum. During voiding, the obstruction caused by the anterior valves dilates the urethral diverticulum just proximal to the valves. This phenomenon in its turn undermines and compresses the dilated proximal urethra, resulting in further increased obstruction. Other authors believe that the diverticulum is the primary lesion and that, with progressive enlargement, the distal lip becomes more mobile, thereby forming a pseudovalve.

Anterior valves can be located anywhere in the urethra. One third are found in the bulbar urethra, one third in the penoscrotal junction, and one third in the penile urethra.

The diagnosis is usually made in the newborn period, if the obstruction is severe. If the obstruction is less severe, the patient may present with nonspecific symptoms such as incontinence, dribbling, and urinary tract infections. Some children report typical urethral ballooning, deviating the penis dorsally during micturition.

The diagnosis should be confirmed by an antegrade VCUG. Obstruction demonstrated at the level of the fossa navicularis should not be taken as evidence of "just meatal stenosis" if the meatus is normal on clinical examination. Clinical observation of the voided stream and demonstration of a needle-like stream and ballooning of the penile urethra is helpful and sometimes essential in making the correct diagnosis. Renal ultrasonography is necessary to evaluate the severity of obstruction and reflection on the upper urinary tract.

The treatment should be determined individually, depending on the severity of obstruction. It may be necessary to divert suprapubically in the newborn period. If the associated diverticulum is small, endoscopic incision or resection can be used to treat the valves, and the diverticulum will resolve spontaneously. However, if the obstruction is more significant and the diverticulum does not resolve after incision of the valve, open urethral correction in a second phase is indicated to resect the redundant urethra.

Syringocele, Cowper Duct, and Cysts

The bulbourethral glands are two paired periurethral glands situated in the urogenital diaphragm and along the corpus spongiosum of the bulbomembranous and bulbospongious urethra. They were first described by Mery (1684) and William Cowper (1699).[21] In girls, the homologous glands are known as Bartholin glands. As depicted in Figure 34-9, the ducts are located within the spongiosus tissue and have small openings into the bulbar urethra. The glands normally secrete a fluid that acts as a lubricant for semen during ejaculation. Colodny and Lebowitz[22] were the first to describe reflux of contrast medium into the small ducts during urethrography. In 1983 Maizels and coworkers[23] described a classification of dilations of the gland based on clinical characteristics of eight boys. They also introduced the term *syringocele* (from *syrongos,* meaning "tube," and *cele,* meaning "swelling").

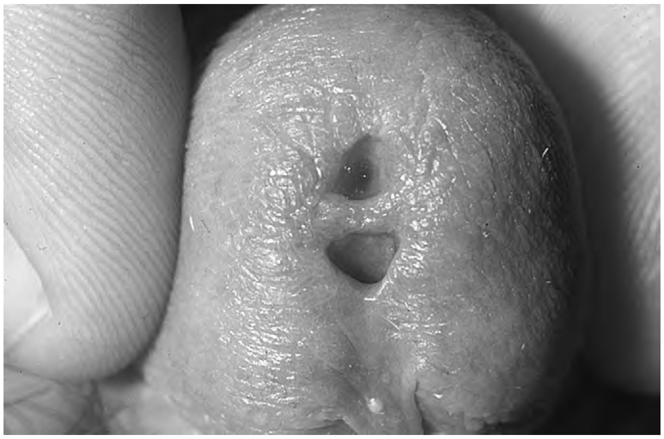


Figure 34-6 This 9-year-old boy has an asymptomatic and blind-ending second epispadiac urethra.

Rarely, a dilated Cowper gland or duct may be seen as a typical syringocele endoscopically within the urethra, because the membrane can be ruptured or perforated very easily. A syringocele (Fig. 34-10) can cause a urethral obstruction in the neonate (Fig. 34-11). More often, abnormalities of the Cowper ducts are asymptomatic and diagnosed only occasionally (2% to 3%).[21] Sometimes, nonspecific symptoms such as dribbling, urgency, urethral obstruction, or hematuria occur.

Reflux into dilated ducts can occur secondary to an anterior obstruction.

The diagnosis of a syringocele or other abnormalities of the Cowper gland or duct is made by antegrade (see Fig. 34-10) or retrograde urethrography and urethroscopy. However, in the situation of late diagnosis, complications such as bleeding or infection may occur. Therefore, in the absence of an abnormal antegrade VCUG or retrograde urethrography and persistent problems such as bleeding or infection, a syringocele or other abnormality of the Cowper gland can be seen by ultrasound of the urethra or by magnetic resonance imaging (Fig. 34-12).

In most cases, spontaneous perforation or rupture requires no further treatment. However, if endoscopic persistence is seen, transurethral incision will solve the problem. Only very few patients require open surgical correction with marsupialization. On rare occasions, secondary dilation due to urethral strictures requires additional or specific treatment.

Urethral Prolapse

Urethral prolapse can occur in young girls. It consists of a mostly painless protrusion of the urethral mucosa. Because it has the clinical characteristic of swelling of the mucosa in the urogenital area (Fig. 34-13A), it is often falsely diagnosed as a vaginal tumor. There is a predominance of incidence in black girls, and the exact cause of the problem is unknown. The most evident hypothesis for urethral prolapse is poor attachment

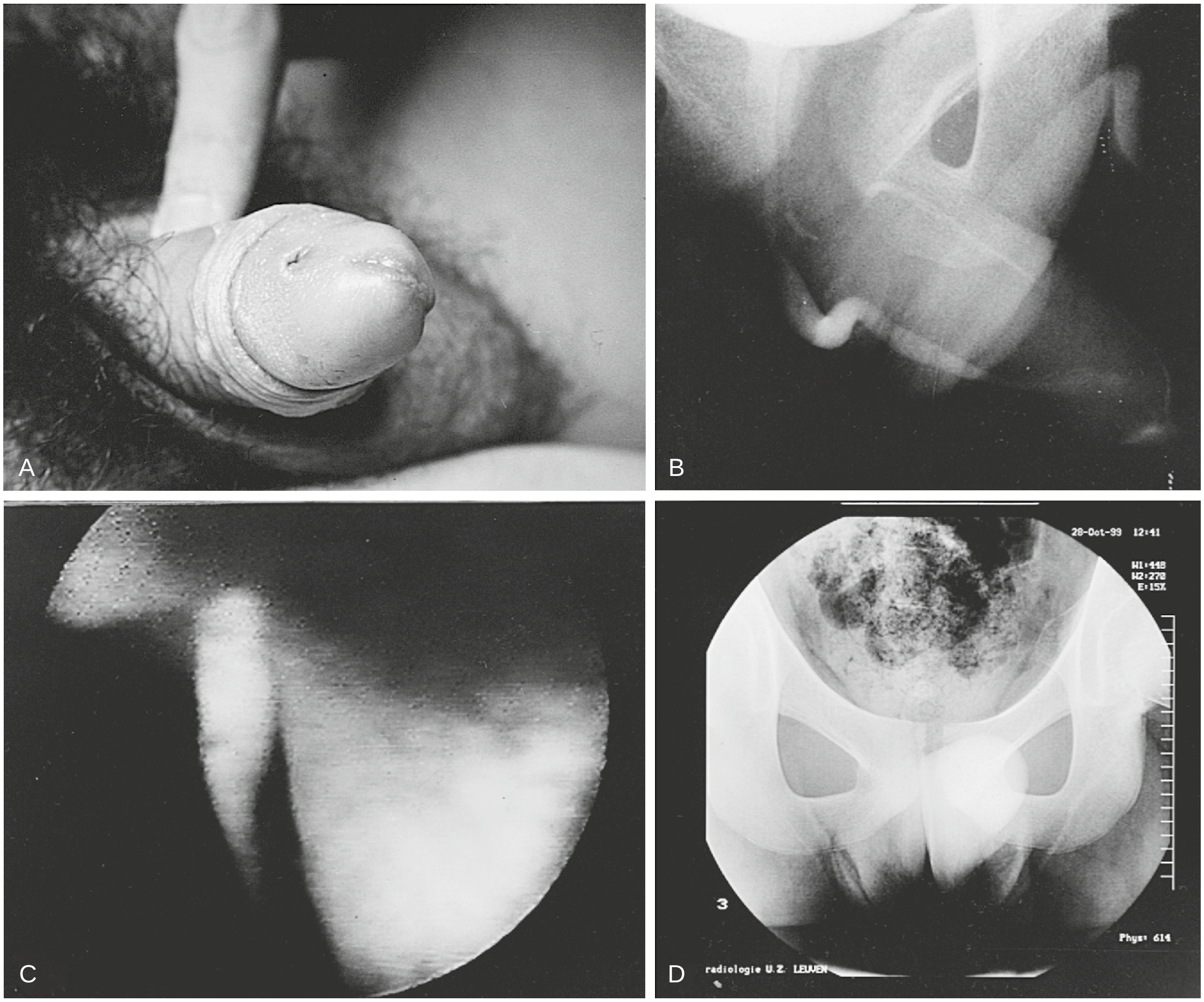


Figure 34-7 A 16-year-old boy presented with recurrent urinary infections and a second epispadiac meatus. However, his first urinary infection was discovered during his stay in the maternity ward as a neonate. He had a total circumcision at 12 years of age because of phimosis, and at that time a second opening on the glans was observed dorsally **(A). B,** Voiding excretory urography showed a complete duplication of the urethra. **C,** During urethrocystoscopy, after insertion of a guidewire through the supplementary opening, an additional internal urethral orifice was seen on the level of the bladder neck, ventrolateral left to the orthotopic urethral opening. **D,** On anteroposterior plain radiographic film, the symphysis appears at least 7 mm wider than is normal for his age.

between the smooth muscle layers of the urethra in association with episodic increases in intra-abdominal pressure.

Urethral prolapse can manifest similarly to a urethral polyp, a prolapsed extravesical ureterocele, a periurethral abscess, or a vaginal problem.

The diagnosis is mainly clinical and is completed with endoscopic evaluation.

Conservative treatment should be attempted with Sitz bathing and oral antibiotics. However, in most cases, surgical excision of the prolapse and mucosal adaptation is needed. Placement of a transurethral catheter facilitates the surgical correction and adaptation of the mucosal edges (see Fig. 34-13B). There are rarely any complications or recurrence.

Urethral Polyps

Urethral polyps in girls are extremely rare and may be diagnosed as small, red, painful masses at the urethra. They are probably prolapsing urothelium that have evolved into polyps and therefore can be considered as partial urethral prolapse. The excision, identical to that described for urethral prolapse, is curative.

Urethral Stricture

Strictures can occur in the male or female urethra. They can be congenital or secondary to trauma, infection, or surgery (Table 34-3). In the male, strictures can occur in the posterior urethra (membranous and prostatic tract) and in the anterior urethra (fossa navicularis, penile and bulbar tract).

Seventy-five percent of congenital urethral strictures are located in the pars bulbosa of the male urethra. The explanation can be found in the embryologic development. This is the place where the proximal urethra, derived from endodermal origin, merges with the urogenital membrane. Another explanation for these strictures could be that the urogenital membrane does not retract completely.

Traumatic straddle injuries most frequently lead to bulbar strictures, whereas pelvic injuries and associated ruptures of

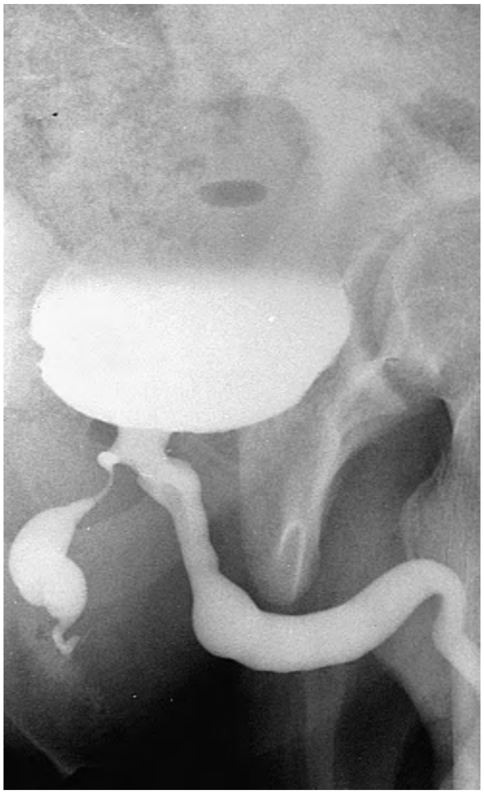


Figure 34-8 Voiding cystourethrogram of an 18-year-old male patient complaining for the first time of anal urinary leakage during micturition. A normal orthotopic urethra and a hypoplastic secondary urethroanal urethra, arising from the prostatic urethra, are seen. The urethroanal urethra was surgically removed and ligated up to the level of the prostate.

the urethra cause strictures in the membranous urethra and in the prepubertal urethra close to the bladder neck.

Surgical urethra strictures are most commonly hypospadias failures and may involve the (new) external meatus or the entire pendulous urethra. They are frequently associated with fistulas, diverticula, stones, hair, cosmetic defects, and residual penile curvature.

Patients with congenital strictures present in either the neonatal or the postpubertal period (between 15 and 25 years).[24,25] In those presenting in the neonatal period, there are significant signs of infravesical obstruction associated with upper urinary tract abnormalities. In contrast, the group of boys who present after puberty have localized irritation symptoms (urinary tract infection, epididymitis, prostatitis, hematuria) and decreased urinary flow. In this older group of patients, no upper tract abnormalities are seen.

The diagnosis of a stricture should be documented during VCUG (Fig. 34-14), either after intravenous pyelography (indirect) or by suprapubic punction (direct). Documentation of urinary flow is important for initial evaluation and follow-up after treatment. If, after these investigations, the diagnosis is uncertain, careful low-pressure retrograde urethrography, eventually in combination with suprapubic punction, can delineate more precisely the extent of the stricture. Ultimately, endoscopic evaluation will diagnose the stricture and set the first step for treatment.

Standard initial treatment consists of sharp cold incision by Sachse urethrotomy.[26] However, if open surgical reconstruction is required, only an individualized approach combining different surgical techniques can lead to success: one or two steps, the possibility and use of pedicled penile skin, the use of buccal mucosa inlay, the presence of surrounding spongiosus tissue (positive in traumatic strictures, negative in post-hypospadias surgery).

In girls, the situation is different. The female urethra has a unique endodermal origin and can be compared with the male prostatic urethra. The meatus opens if the urogenital membrane retracts. Therefore, in girls, the stricture will be located at the site of the meatus.[27]

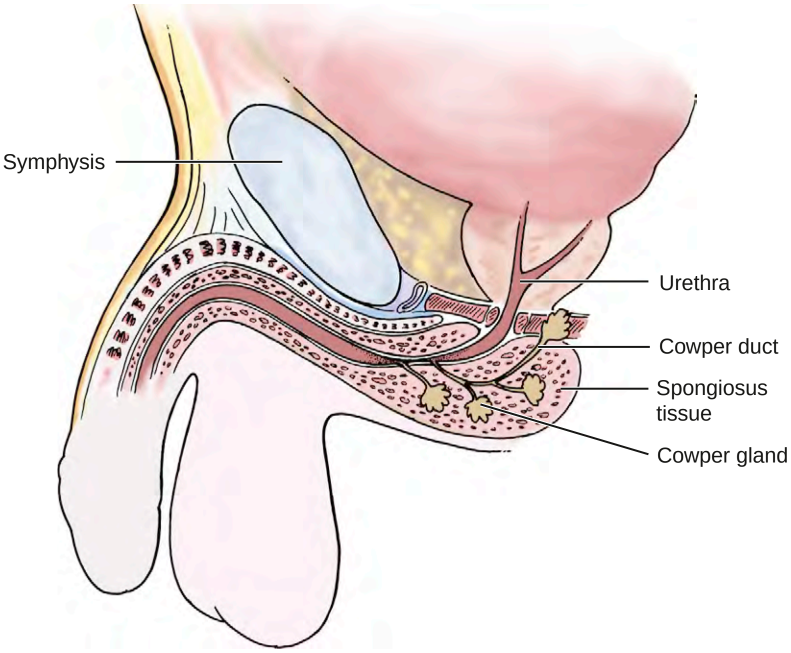


Figure 34-9 Schematic drawing of the Cowper glands and ducts and their relation to the spongiosus tissue and external sphincter.

In 1963, Lyon and Smith[28] reported that they found a meatal stenosis in 90% of girls with recurrent urinary tract infections. In these girls, the stricture consisted of an increase in collagen. Treatment appeared easy and gained popularity because of the numerous reports of disappearance of the recurrent urinary tract infections.[29] However, after a more critical look at the results and elimination of the effect of spontaneous disappearance after medical treatment, this theoretical hypothesis was found to be not valid.[30] Today, most of the problems of recurrent urinary tract infections and reflux can be correlated with dysfunctional voiding.[31] Stenosis due to an anatomic stricture is extremely rare.

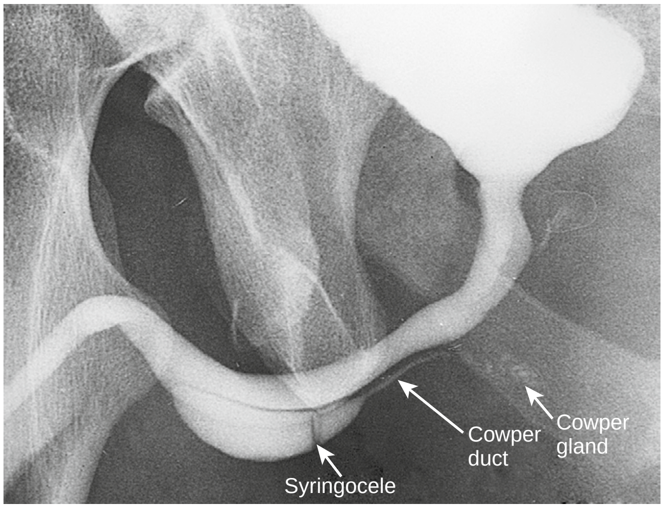


Figure 34-10 Image obtained during voiding (antegrade voiding cystourethrogram) demonstrates clearly a syringocele and the Cowper ducts and glands.

The diagnosis of meatal stenosis or stricture in girls is made by calibrating the urethra using bougie à boule. With pulling distally, a stenosis appears as a white ring (mucosal ischemia). The normal size of the female urethra depends on the age of the child, and the reference values of Immergut and Wahman[2] are still universally accepted.

The treatment options are dilation and Otis urethrotomy. Although the incidence of stress incontinence or recurrence of stricture after urethrotomy appears to be low, one should be very well aware of these serious complications.

It should be emphasized that meatal stenosis in girls is extremely rare. Routine investigation or treatment such as urethrotomy can cause serious long-term complications and should be avoided.

Urethrorrhagia Idiopathica and Urethritis Posterior in Prepubertal and Pubertal Boys

Urethrorrhagia idiopathica and *urethritis posterior* refer to the same condition, but the former term is used more frequently in American literature. This phenomenon occurs frequently and alarms many prepubertal and pubertal boys and their parents. At the end of micturition, a few drops of blood appear at the meatus, frequently associated with a painful irritative sensation within the urethra. The intense blood color staining of the underwear also causes alarm. Sometimes, boys report gross hematuria, so a careful history and distinct examination of midstream and endstream urine are important to recognize this phenomenon.

Bleeding from localized irritated mucosal changes in the bulbar urethra just distal to the external sphincter causes this condition. There are sometimes areas of leukoplakia. If special attention is taken during urethroscopy, one might observe thin fibrin membranes covering these areas. Histologically, metaplasia of the basal epithelial cells containing keratin is found.[32] These cells have an estrogen level–dependent proliferation capacity and can interfere with the other epithelial cells. The condition occurs in boys at the onset or during puberty. In some of these boys, a higher

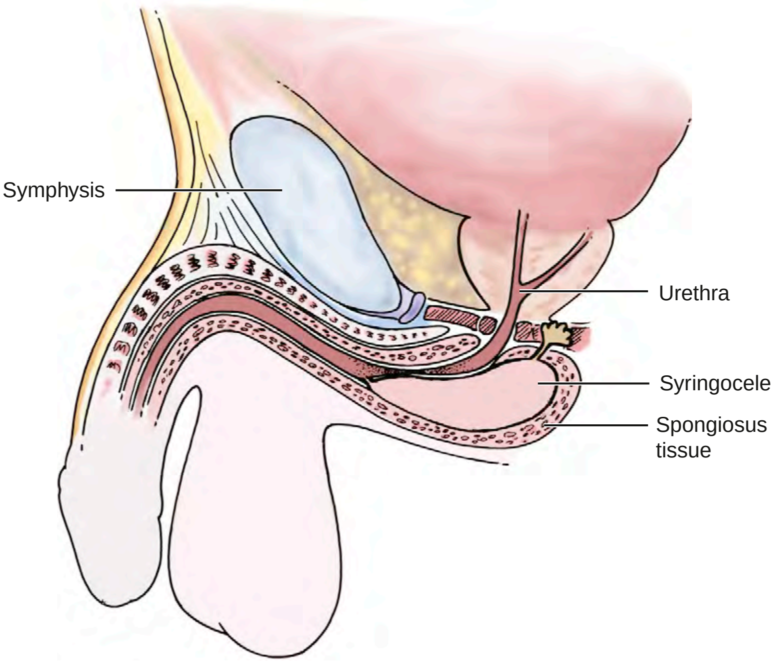


Figure 34-11 Schematic drawing of a closed dilation of a Cowper duct within the bulbospongiosus urethra (bulbar form of a closed syringocele). This can cause flow impairment and can act as a subvesical obstruction.

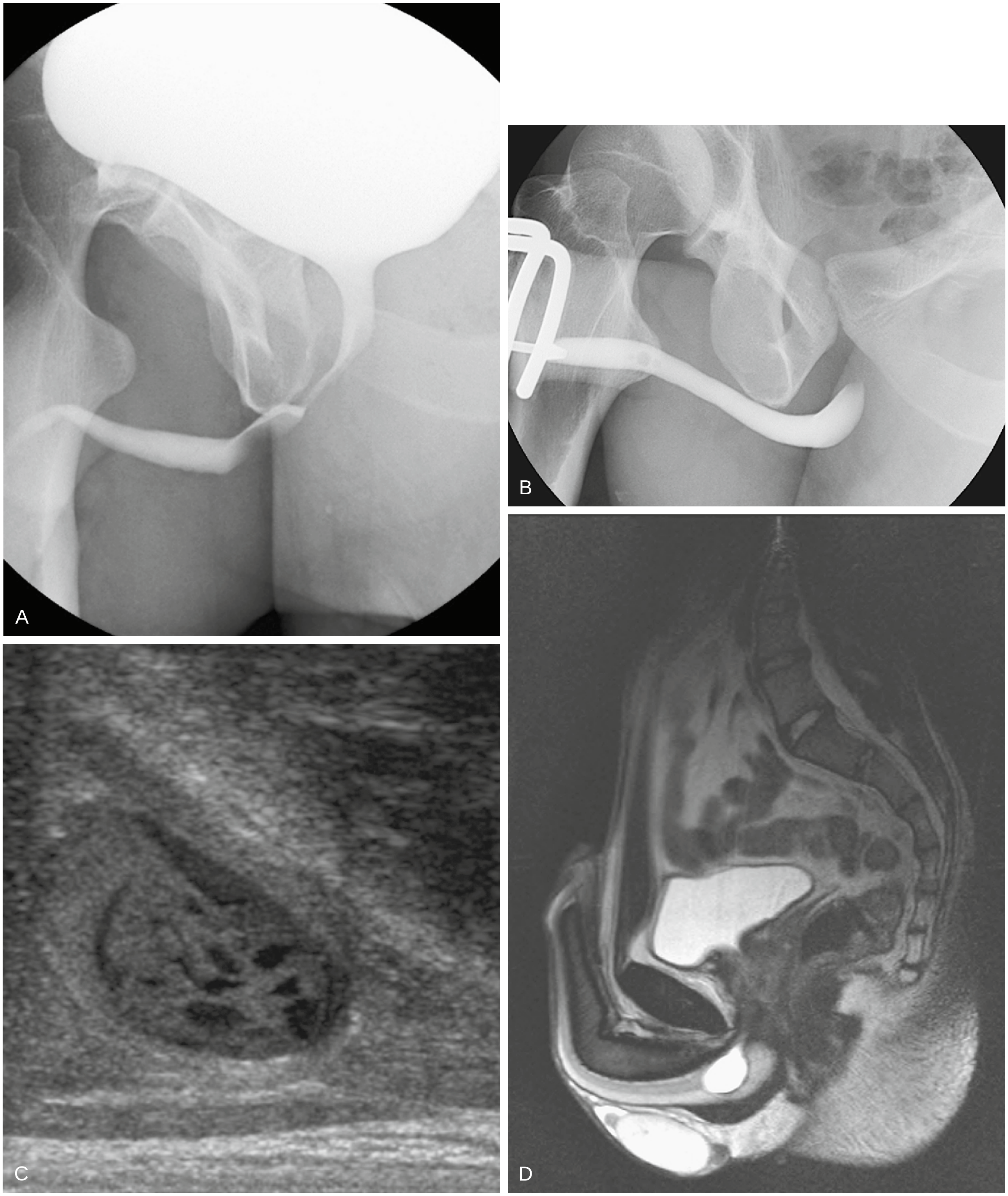


Figure 34-12 **A,** Image obtained during voiding cystourethrography clearly demonstrates a syringocele. **B,** In the same patient, a retrograde urethrogram demonstrates a normal urethra. **C,** Image obtained by ultrasonographic scanning of the urethra demonstrates an inhomogeneous content of the syringocele and suggests either bleeding or pus. **D,** Magnetic resonance imaging scan of the same patient demonstrates the syringocele and its relation to the urethra, spongiosus tissue, and cavernosal bodies.

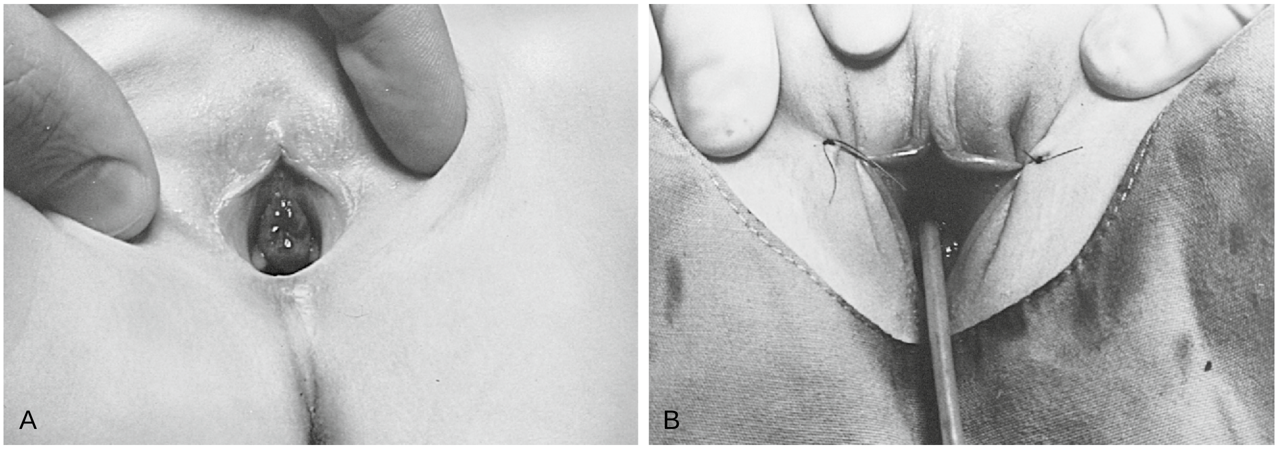


Figure 34-13 **A,** A 3-year-old girl presented with an asymptomatic urethral prolapse. **B,** A catheter was placed to facilitate the surgical removal and adaptation of the mucosal edges.

Table 38-3 **Location and Etiology of Urethral Strictures**

Etiology	Location
Congenital	Bulbar
Trauma: straddle injury	Bulbar
Trauma: pelvic injury	Membranous and prostatic
Infectious	Anterior up to bulbar

serum estrogen level can be found, which explains why this phenomenon occurs at puberty, although a definite explanation is not known.[33]

The diagnosis should be suspected based on the typical history. Microscopic examination of midstream and endstream urine should further confirm the suspected diagnosis. In addition, a detailed ultrasonographic investigation of the kidneys and bladder should be able to exclude pathologic conditions. Because there are no specific radiographic signs and urethral catheterization can cause further irritation and induce fibrosis, there is no indication to perform VCUG or retrograde urethrography. For the same reasons, urethrocystoscopy is not indicated, although it might be the sole chance to confirm the suspected diagnosis of urethritis posterior.

In the differential diagnosis of blood dripping from the meatus (outside the micturition), a bleeding from a lacuna magna should also be considered. A lacuna magna occurs when the fossa navicularis (ectoderm) does not directly reach the distal urethra (endoderm), resulting in a small lacuna or diverticulum. In this situation, the diagnosis is made during VCUG, and sometimes this test is necessary to make the diagnosis if the clinical findings are not clear. With bleeding from a lacuna magna, endoscopic marsupialization by endoscopic cautery is necessary to solve the problem.

Urethrorrhagia caused by urethritis posterior in prepubertal and pubertal boys is a benign condition that disappears spontaneously. It is sometimes necessary to perform a cautious urethrocystoscopy to reassure the boy and his family and to exclude the presence of a lacuna magna in the distal urethra.

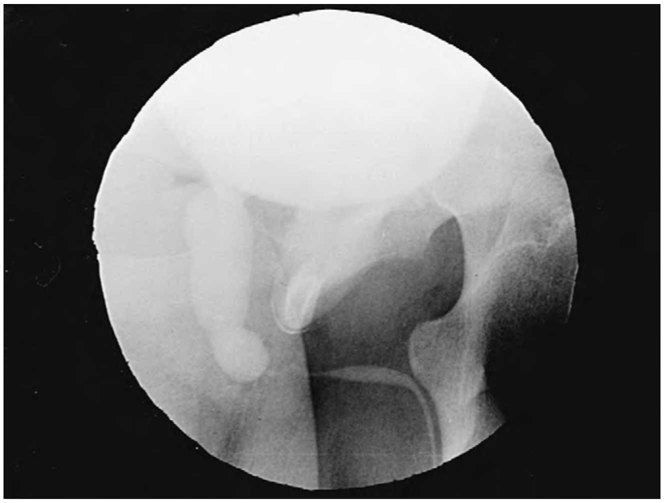


Figure 34-14 Voiding cystourethrogram of a boy presenting with a congenital urethral stricture diagnosed after a febrile urinary tract infection.

Megalourethra

A congenital megalourethra is an enlargement of the pendulous urethra without evidence of distal obstruction. It should be differentiated from acquired megalourethra, which is most frequently caused by a complication of the transverse preputial island flap urethroplasty in boys with hypospadias or the epispadias-exstrophy complex. Dorairajan[34] described two forms of congenital megalourethra based on the shape and extent of associated defects of erectile tissue (Fig. 34-15):

1. Fusiform type: the ectatic urethra has a focal absence of corpus cavernosum and corpus spongiosum.
2. Scaphoid type: the ectatic urethra has a focal absence of corpus spongiosum but is dorsally splinted by intact corpus cavernosum.

The degree of dilation varies. There is no uniform explanation, although speculations are made involving temporary obstruction of the distal fetal urethra or a mesenchymal defect. The latter could explain the fact that a megalourethra is associated with other severe (mesenchymal) anomalies such as the prune-belly syndrome, cloacal anomalies, imperforated anus,

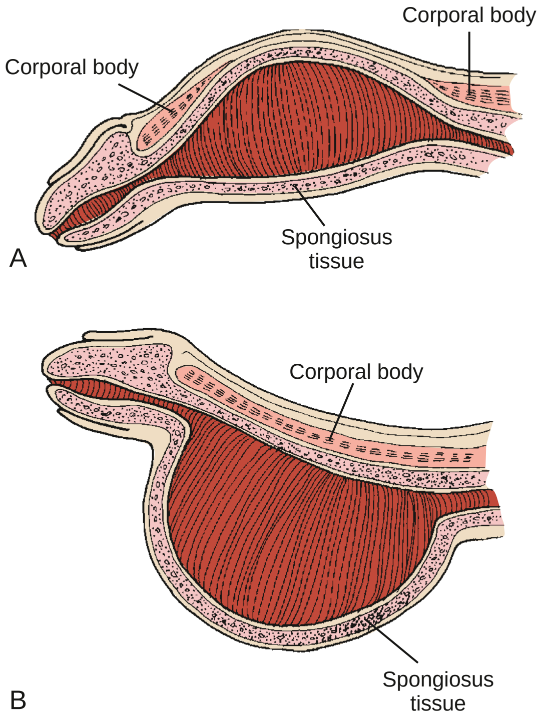


Figure 34-15 Schematic drawing of the two types of congenital megalourethra. **A,** Fusiform type shows a defective corpora cavernosa. **B,** Scaphoid type has an intact, although thinner, corpora cavernosa.

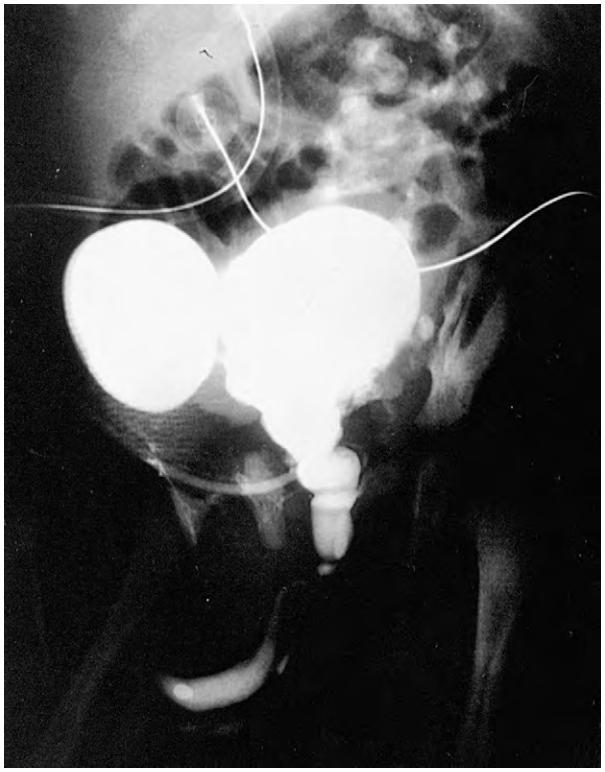


Figure 34-16 Male newborn with the VACTERL (*v*ertebral abnormalities, *a*nal atresia, *c*ardiac abnormalities, *t*racheoesophageal fistula and *e*sophageal atresia, *r*enal agenesis and dysplasia, and *l*imb defects) syndrome and a urethral duplication. In addition, the dorsal urethra has the aspect of a megalourethra. Note also the bladder diverticulum.

refluxing megaureters, and the VACTERL (*v*ertebral abnormalities, *a*nal atresia, *c*ardiac abnormalities, *t*racheoesophageal fistula and *e*sophageal atresia, *r*enal agenesis and dysplasia, and *l*imb defects) syndrome (Fig. 34-16).[35] The diagnosis is mainly clinical, but VCUG or retrograde urethrography can exclude other urethral anomalies.

The treatment consists of resection of the redundant urethral mucosa. This is possible if normal dorsal corpus cavernosum is present and acts as a dorsal support. With a fusiform urethra, repair would be difficult but is often unnecessary, because these patients do not survive owing to the other severe anomalies.

REFERENCES

For complete list of references log onto www.expertconsult.com

PART VI

GENITALIA

SECTION 1

AMBIGUOUS GENITALIA

CHAPTER 35

DISORDERS OF SEX DEVELOPMENT: ENDOCRINE ASPECTS

Claire Bouvattier

Disorders of sex development, a less pejorative term than "intersex," encompass a range of inborn errors of metabolism and dysmorphisms, having in common anomalous genitalia. Normal sex development consists of three sequential processes. Genetic sex is determined from the moment of conception by the sex chromosome constitution. Then, the undifferentiated gonad differentiates into either a testis or an ovary (gonadal determination). Finally, sex phenotype is the result of male differentiation, which is an active process resulting from testicular secretions (Figs. 35-1 and 35-2).[1,2] In the literature, disorders of sex development are variable, related to the small numbers in some series, varying definitions of etiologic categories, and even exclusion of so-called idiopathic cases. Actual prevalence figures are unknown, with population estimates ranging between 1 in 4500 and 1 in 50, depending on definitions.

It is important to recognize all sex development disorders as early as possible in life and not to delay the etiologic diagnosis. The diagnosis should be as precise as possible, to promote institution of substitutive treatment in case of an enzymatic defect in steroid biosynthesis, but should also help to determine the choice of the most appropriate gender of rearing. Investigations should evaluate the chances of the best somatic and psychological development in the sex assigned. In contrast to 46,XX virilized girls, the cause in the majority of 46,XY patients undermasculinized at birth remains unknown.

Despite advances in understanding gonadal differentiation and increased accuracy of diagnosis, the clinical management of disorders of sex development has changed little. Genital surgery is now one of the most controversial interventions in intersex management.[3] In the absence of clinical trials and with minimal objective cohort studies providing data on outcomes for cosmetic, gender, social, or sexual function after this surgery, together with anecdotal evidence of dissatisfaction among adult patients who underwent childhood surgery, clinicians and parents face huge dilemmas.[4] Current theories of gender development postulate that both prenatal factors (testosterone) and postnatal factors (social environment) are important, and that genital appearance is less relevant. However, clinicians remain uneasy about gender development if the genitals remain uncorrected and are concerned about possible psychological distress from bullying if a child has an abnormal genital appearance. Even if multidisciplinary teams now manage patients with disorders of sex development, we need to rethink our approach to the management of intersex conditions.[5]

PHYSIOPATHOLOGY

The first step in prenatal sexual development starts with the chromosomal complement. Most males possess a 46,XY chromosome complement, and most females 46,XX. Up to the 8th week of gestation, human reproductive organs show no sign of sex differentiation and consist of unipotential wolffian and müllerian ducts and bipotential sinusal and external genital primordia (Fig. 35-3). Wolffian ducts are the excretory canals of the primitive kidney, the mesonephros, and they are incorporated into the genital system when renal function is taken over by the metanephros, or definitive kidney. Müllerian ducts arise from a cleft lined by coelomic epithelium that originates between the gonadal ridge and the mesonephros and grow caudally. The undifferentiated external genitalia are represented by the genital membranes, which close the ventral part of the cloaca and are surrounded ventrally by the genital tubercle and laterally by the genital folds or labioscrotal swellings (see Fig. 35-3). After the corpora cavernosa and glans have differentiated, the genital tubercle elongates to form the phallus, whose ventral surface is depressed by a deep furrow, the urethral groove. The first step of somatic male differentiation is müllerian duct regression, which begins at 8 weeks (see Fig. 35-1). The time during which the presence or absence of the fetal testis affects müllerian anatomy is a critical period. In the human, the müllerian ducts have almost completely disappeared by 10 weeks of gestation.

The second aspect of internal male differentiation is the integration of wolffian ducts into the genital system and their

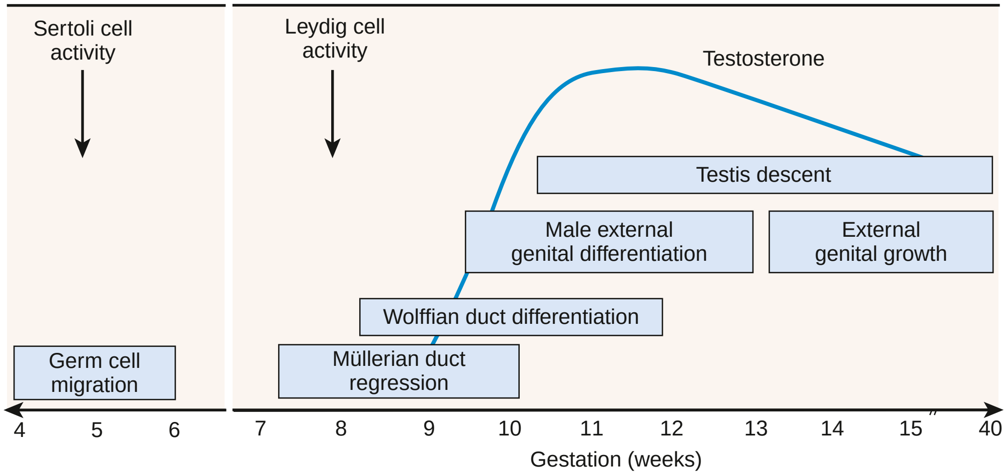


Figure 35-1 Schematic embryology of male sex development. The curve depicts the relative concentration of fetal serum testosterone.

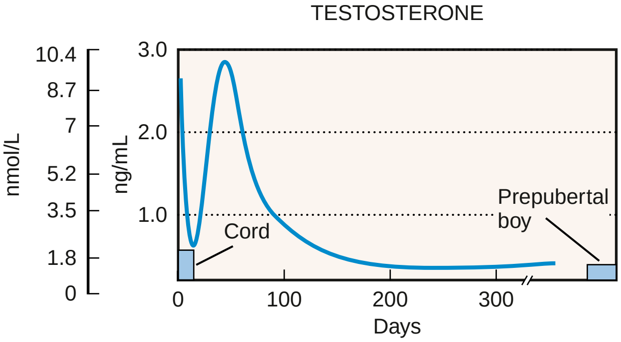


Figure 35-2 Postnatal testosterone peak in normal 46,XY males.

development into epididymides, vasa deferentia, and seminal vesicles. Male orientation of the urogenital sinus is characterized by prostatic development and repression of vaginal development. Masculinization of the external genital organs begins at 10 weeks with lengthening of the anogenital distance, followed by fusion of the labioscrotal folds and closure of the rims of the urethral groove, leading to the formation of a perineal and penile urethra. Penile organogenesis is complete by 80 days of gestation, but until the 16th week the penis and clitoris are more or less the same size.

As was shown by Jost,[6] two hormones are required to drive male differentiation of the reproductive tract (Fig. 35-4). Regression of the müllerian ducts is programmed by antimüllerian hormone (AMH), which is secreted by primitive Sertoli cells immediately after testicular differentiation. Virilization of the urogenital sinus and external genitalia is caused by testosterone, which is produced from cholesterol by steroidogenic enzymes expressed by fetal Leydig cells, starting from the 9th week of gestation. Testosterone is metabolized into dihydrotestosterone (DHT) by the enzyme 5α-reductase. Both testosterone and DHT bind to the androgen receptor (AR).

CLASSIFICATION OF THE SEX DEVELOPMENT DISORDERS

Classification of the sex development disorders is based on the recognition of the underlying anomaly in the process of sexual differentiation. In males, intersexuality may be divided into abnormal gonadal determination and abnormal genital differentiation. Gonadal determination, the process that drives testicular differentiation; requires a normal component of virilizing genes on the Y chromosome and also on autosomes (Fig. 35-5). Because virilization of the fetal reproductive tract depends on testicular hormones, the presence of testicular dysgenesis or heterogeneous gonadal differentiation, like true hermaphroditism, leads to a combined defect in both AMH and testosterone.

Persistence of müllerian derivatives associated with hypospadias is highly evocative of testicular dysgenesis, but the time of onset of testicular degeneration may influence clinical symptoms. In contrast, disorders of testicular differentiation affect a single testicular hormone. 46,XY undervirilized males (male pseudohermaphroditism) have ambiguous genitalia but two differentiated testes, resulting from abnormal testosterone biosynthesis or metabolism or androgen receptor defects. 46,XX virilized females (female pseudohermaphroditism) have ambiguous external genitalia but normal ovaries and normal internal genitalia, resulting from in utero exposure to abnormal levels of androgens at the critical time of sex differentiation.

The disorders of sex development may be classified according to our knowledge of the genetic basis of sex determination and differentiation (Tables 35-1 and 35-2). In most disorders, there is a wide range of presenting phenotypes.

INVESTIGATION AND MANAGEMENT OF SEX DEVELOPMENT DISORDERS

The observation of ambiguous genitalia is a medical and psychological emergency. The normally routine announcement of the baby's gender cannot be made to the parents, and its future identity, which is in great part based on gender, will be held in suspension until the most appropriate sex of rearing is chosen. The goal of the physician is to establish a diagnosis and assign a sex for rearing that is the most compatible with a well-adjusted life and sexual adequacy. Once the sex is assigned, the gender role is reinforced by the use of appropriate hormonal and psychological measures.

Abnormalities of sex differentiation should be suspected not only in infants with ambiguous genitalia but also in phenotypic females with palpable gonads, inguinal hernia, slight clitoral enlargement, posterior labial fusion, or a single perineal orifice. Also, phenotypic males without palpable gonads

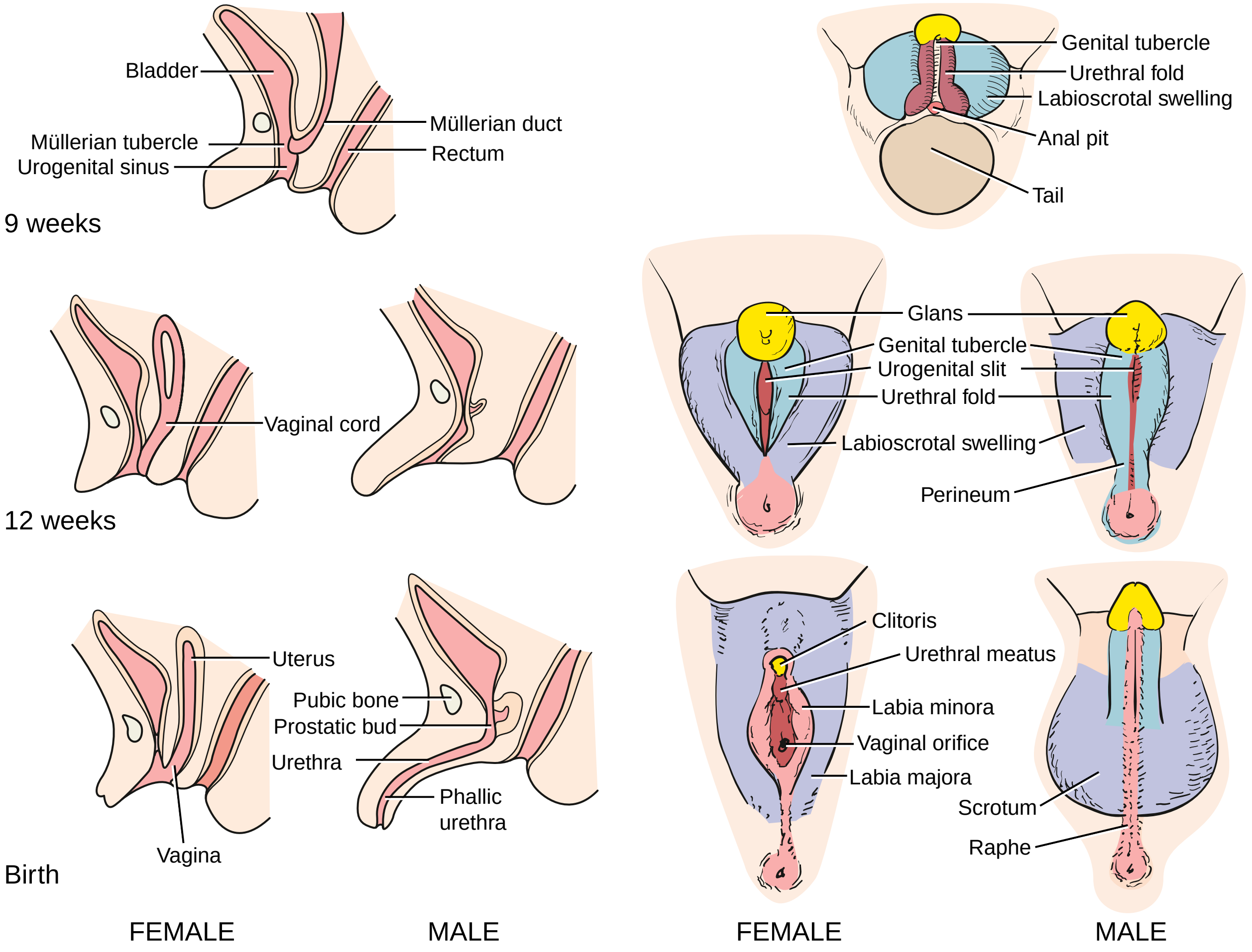

Bladder
Müllerian tubercle
Urogenital sinus
Müllerian duct
Rectum
9 weeks
Vaginal cord
12 weeks
Uterus
Pubic bone
Prostatic bud
Urethra
Phallic urethra
Vagina
Birth
FEMALE
MALE
Genital tubercle
Urethral fold
Labioscrotal swelling
Anal pit
Tail
Glans
Genital tubercle
Urogenital slit
Urethral fold
Labioscrotal swelling
Perineum
Clitoris
Urethral meatus
Labia minora
Vaginal orifice
Labia majora
Scrotum
Raphe
FEMALE
MALE

Figure 35-3 Differentiation of the urogenital sinus *(left)* and external genitalia *(right)*.

and those with hypospadias or unusually small genitalia or gonads must be carefully studied.

Details of the pregnancy, including exposure to androgens, progestins, and estrogens and maternal virilization during pregnancy, should be sought. Consanguinity should be ascertained, as well as family history (e.g., recessively inherited congenital adrenal hyperplasia, X-linked androgen insensitivity), including unexplained neonatal deaths, amenorrhea, and infertility. The neonate may have come to attention prenatally after detection of an abnormal karyotype or suspicious ultrasound evidence of a genital abnormality. Careful clinical examination of the infant should assess the presence of dysmorphic features and hyperpigmentation. The location of the gonads is important, and a palpable gonad most likely indicates the presence of testicular tissue. Asymmetry of the gonads and external genitalia occurs in partial gonadal dysgenesis and in true hermaphroditism. Care must be taken to ensure that measurements of the length of phallus are taken to the tip of the glans. Varying degrees of hypospadias, with a urethral opening on the glans, penile shaft, or perineum, can occur. Hypospadias may be accompanied by a curvature of the penis, which may give the false impression that the phallus is shorter than it actually is. Separate urethral and vaginal openings should be noted in the normal female. A urogenital sinus, with a single canal that drains the genital and urinary systems, commonly occurs in congenital adrenal hyperplasia (CAH). Anorectal anomalies may be associated with renal, genital, and gastrointestinal abnormalities. Degrees of genital ambiguity can be described using the Prader scale, which was originally devised to describe the degree of virilization of female genitalia in CAH (Fig. 35-6).

Fluorescent in situ hybridization (FISH) for Y chromosome or peripheral karyotype analysis is an imperative step. Initial hormonal studies including plasma 17-hydroxyprogesterone, Δ^4-androstenedione, dehydroandrostenedione (DHAS), testosterone, and DHT are the keys to the etiologic diagnosis of steroid enzyme defects (Fig. 35-7). The initial investigations also include serum electrolytes and determination of plasma or serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and AMH. Pelvic ultrasound is useful for assessing the presence of the uterus and any müllerian or wolffian structures that may be present. The uterus is particularly prominent in the neonatal period, under the influence of maternal and placental hormones. Imaging could also include magnetic resonance scans of the kidneys, ureter, and pelvic contents. Urogenital sinography, which involves retrograde injection of contrast material into the urogenital sinus opening, is used to delineate the anatomy of the lower vagina.

UNDERVIRILIZED MALES: SPECIFIC DIAGNOSIS

An algorithm for etiologic diagnosis in undervirilized male infants is presented in Figure 35-8.

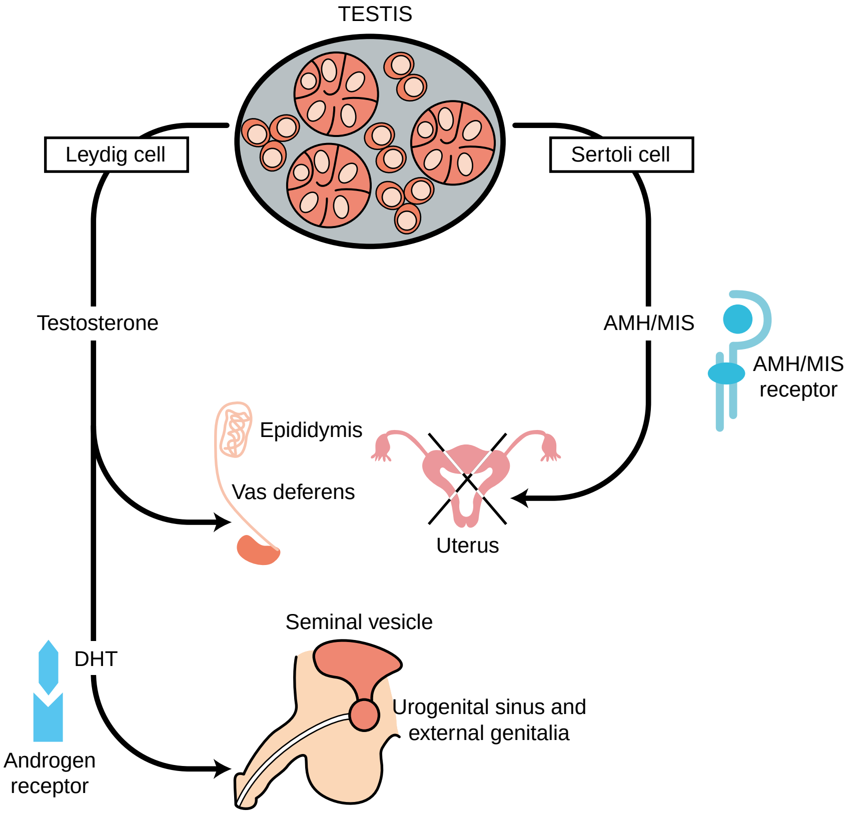


Figure 35-4 Hormonal control of sex differentiation by testosterone and anti-müllerian hormone (AMH). DHT, dihydrotestosterone; MIS, müllerian inhibiting substance.

Abnormalities in Early Gonadal Determination: Syndromes of Gonadal Dysgenesis

Gonadal dysgenesis is characterized by abnormal testicular determination. However, 46,XY gonadal dysgenesis syndrome is clinically and genetically heterogeneous. It can be sporadic or familial. Phenotypic differences can be observed depending on the extent of testicular development, and a continuum of phenotypes ranging from female phenotype to ambiguous external genitalia has been described. Variable expressivity has been reported within families as well.[7] Several situations of 46,XY sex reversal have resulted from mutations in genes controlling the primordial gonad and the bipotential reproductive ducts (see Fig. 35-5).

Gonadal Dysgenesis and Adrenal Abnormalities: Steroidogenic Factor 1

Steroidogenic factor 1 (SF1) is an orphan nuclear hormone receptor that is expressed early throughout the hypothalamic pituitary gonadal axis.[8] It is essential for normal adrenal and gonadal development, as predicted from targeted disruption of the gene in mice. The function of SF1 is not clear, but it may regulate the regression of the müllerian structures.[9] The first case of mutation in the gene encoding SF1 was reported in 1999.[10] Fewer than 10 patients have been described, usually 46,XY phenotypically female individuals with primary adrenal failure in the first weeks of life. Before puberty, testosterone shows no response after human chorionic gonadotropin (hCG) stimulation. Streak gonads and normal müllerian structures are present. A heterozygous SF1 mutation has been identified in a 46,XY patient with partial gonadal dysgenesis and normal adrenal function.[11]

Gonadal Dysgenesis and Renal Abnormalities: Wilms' Tumor Suppressor Gene

Wilms' tumor suppressor gene (*WT1*) encodes a four contiguous zinc-finger–containing protein that is involved in the regulation of DNA transcription. The gene is alternatively spliced, and 24 protein isoforms can be detected in the developing kidney, genital ridge, fetal gonads, and mesothelium.

Chromosomal deletions at 11p13 were first identified in patients suffering from a contiguous gene syndrome known as *WAGR syndrome* (*W*ilms' tumor, *a*niridia, *g*enitourinary abnormalities, and mental *r*etardation).[12,13]

In humans, *WT1* heterozygous point mutations are associated with the *Denys-Drash syndrome*, which is characterized by genital abnormalities, glomerular nephropathy, and Wilms' tumor.[14-17] Individuals with Denys-Drash syndrome have a female phenotype or ambiguous genitalia and dysgenetic gonads. The nephropathy is characterized by proteinuria at an early age evolving into nephrotic syndrome and renal failure due to focal glomerular and mesangial sclerosis. Wilms' tumor develops early in life and is frequently bilateral. A *WT1* heterozygous mutation was identified in an undermasculinized newborn infant with glomerular lesions, no Wilms' tumor, and a large diaphragmatic hernia.[18] Systematic mutational screening of the *WT1* gene in severe hypospadias should be done, even in the absence of endocrine abnormality or Wilms' tumor.[19]

The *Frasier syndrome* is a variant of the Denys-Drash syndrome. Affected individuals have 46,XY complete gonadal dysgenesis and late-onset nephropathy.[20] Glomerular symptoms consist of childhood proteinuria and nephrotic syndrome, characterized by unspecified focal and segmental glomerular sclerosis, progressing to end-stage renal failure in

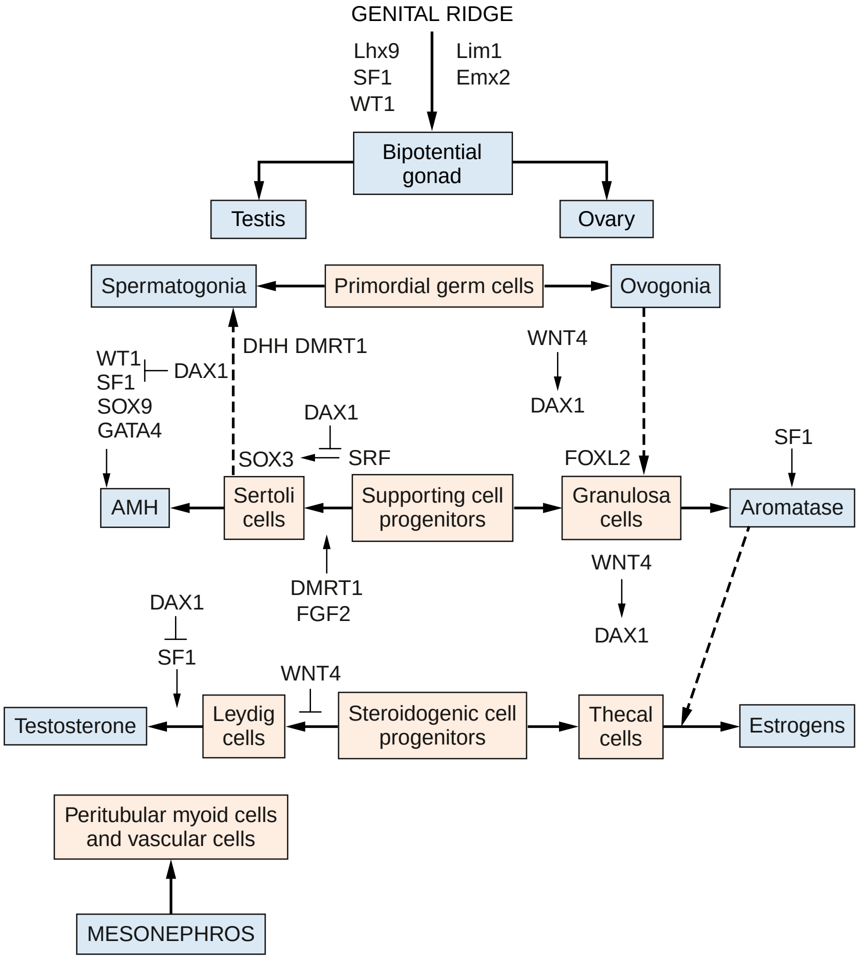

GENITAL RIDGE
Lhx9
SF1
WT1
Lim1
Emx2
Bipotential gonad
Testis
Ovary
Spermatogonia
Primordial germ cells
Ovogonia
DHH DMRT1
WT1
SF1
SOX9
GATA4
DAX1
WNT4
DAX1
DAX1
SOX3
SRF
FOXL2
SF1
AMH
Sertoli cells
Supporting cell progenitors
Granulosa cells
Aromatase
DMRT1
FGF2
WNT4
DAX1
DAX1
SF1
WNT4
Testosterone
Leydig cells
Steroidogenic cell progenitors
Thecal cells
Estrogens
Peritubular myoid cells and vascular cells
MESONEPHROS

Figure 35-5 Genetics of male sex determination. (Accessed from www.medscape.com. Source: Semin Reprod Med © 2002 Thieme Medical Publishers.)

adolescence or early adulthood. Frasier syndrome is caused by mutations in the donor splice site in intron 9 of *WT1*.[21-23]

Gonadal Dysgenesis and SRY*: 46,XY Pure Gonadal Dysgenesis*

First described by Swyer, 46,XY pure gonadal dysgenesis is the association of female phenotype, female internal genitalia, normal or tall stature, and sexual infantilism with primary amenorrhea.[24] These patients have streak gonads, which do not secrete testosterone or AMH. Primary amenorrhea with hypergonadotropic sexual infantilism is the most frequent presenting symptom in a girl with a normal or tall stature. Ultrasonography and gynecologic examination demonstrate a uterus.[25] The genetics of XY sex reversal is heterogeneous.[26,27] Mutations of the sex-determining region Y *(SRY)* gene have been described in sporadic cases resulting from de novo mutation[28-30] and in familial cases,[31] but these account for only an estimated 15% to 20% of 46,XY females.[32,33] In 46,XY pure gonadal dysgenesis, pubertal development should be initiated by estrogen replacement therapy. Because of the high risk of dysgerminoma, seminoma, and gonadoblastoma, prophylactic removal of the streak gonads with histologic examination is advised.[34]

Patients with *partial gonadal dysgenesis* have a mix of wolffian and müllerian duct derivatives and some functional capacity to produce testosterone or AMH or both. Gonadal tissue may contain areas of poorly differentiated seminiferous tubules in combination with areas of ovary-like stroma.[35] In the incomplete form, assignment of a male gender role may be possible, depending on the degree of virilization of the genitalia.

Gonadal Dysgenesis and Skeletal Abnormalities: SOX9 *Gene*

Camptomelic dysplasia is a rare, often lethal, dominantly inherited, congenital osteochondrodysplasia in which three-quarters of the 46,XY patients show female phenotype. The designation “camptomelic dwarfism,” proposed by Maroteaux, comes from the congenital bowing of the legs, especially the tibias. The scapulas are very small, and the pelvis and spine show changes. Eleven pairs of ribs are usually present. Cleft palate, micrognathia, flat face, and hypertelorism are additional features.[36,37] The syndrome includes severe respiratory distress, and most affected patients die in the neonatal period. *SOX9* is a member of the SRY-box–related family and is one of the critical genes in male sexual differentiation. Camptomelic dysplasia is associated with either heterozygous *SOX9* mutations that result in severely truncated proteins or chromosomal translocations that delete upstream regulatory elements. The hypothesis is that camptomelic dysplasia results from haploinsufficiency of *SOX9*.[38,39]

Table 35-1 Classification of Disorders of Sex Development

- **Virilization of 46,XX Females**
- Increased fetal adrenal androgen production
  - Congenital adrenal hyperplasia (21-hydroxylase deficiency, 3β-HSD deficiency, 11β-hydroxylase deficiency)
  - Androgen-secreting tumor
- Fetal gonadal androgen production
  - True hermaphroditism
- Transplacental passage of androgens
  - Drugs administered during pregnancy (progesterone, danazol)
  - Maternal androgen-secreting tumor (luteoma of pregnancy, adrenal tumor)
  - Aromatase deficiency, cytochrome P450 oxidoreductase deficiency (PORD)
- **Undervirilization of 46,XY Males**
- Defective development or maintenance of the testis: testicular dysgenesis
  - Pure (complete) 46,XY dysgenesis
  - Mixed (partial) gonadal dysgenesis 45,X/46,XY
  - Dysgenetic pseudohermaphroditism
  - Testicular regression syndromes (agonadism, vanishing testis)
  - 46,XX males
- Decreased fetal androgen biosynthesis
  - Leydig cell hypoplasia
  - Inborn errors of testosterone biosynthesis (StAR, 3β-HSD, 17α-hydroxylase/17,20 lyase, 17β-HSD, Smith-Lemli-Opitz syndrome)
  - 5α-reductase deficiency
- Decreased fetal AMH production or action
  - Persistent müllerian duct syndrome
- Defect in androgen action
  - Androgen receptor and postreceptor defects (PAIS, CAIS)
- Urogenital malformations, dysmorphic syndromes

AMH, anti-müllerian hormone; CAIS, complete androgen insensitivity syndrome; HSD, hydroxysteroid dehydrogenase; PAIS, partial androgen insensitivity syndrome; StAR, steroidogenic acute regulatory protein.

Gonadal Dysgenesis and Neurologic Abnormalities: α-Thalassemia Mental Retardation Syndrome and Autosomal Deletions

The α-thalassemia mental retardation syndrome (*ATR-X syndrome*) is an X-linked disorder characterized by α-thalassemia, severe mental retardation, and multiple congenital abnormalities which may include 46,XY gonadal dysgenesis and undermasculinization.[40] The gene responsible for the ATR-X syndrome is a DNA helicase termed *ATRX,* which consists of 35 exons. The predicted protein has three zinc-finger binding motifs and may function as a transcription factor.[41]

Sex reversal in 46,XY individuals has been described in association with *chromosome 9p deletions.*[42,43] Studies identified a human domain-containing protein, encoded by a gene that maps to 9p24.3. This protein is known as DMRT1. A similar protein whose gene maps in the same region is termed DMRT2.[44] The human 9p deletion syndrome is characterized by varying degrees of 46,XY sex reversal, mental retardation, and craniofacial abnormalities. Deletion of DMRT1 and DMRT2 in 46,XY individuals leads to sex reversal. This suggests that the mechanism is haploinsufficiency.

Abnormal sex determination has also been found in children with terminal deletion of chromosome 10p.[45]

Gonadal Abnormalities and Duplications: Xp (DAX1) *and 1p* (WNT4)

Reports of *duplications of part of the short arm of X chromosome* in some 46,XY females led to this region's being termed the "dosage-sensitive sex reversal locus," or DSS. Xp21.3 was also the region of interest for another syndrome, consisting of hypogonadotropic hypogonadism and adrenal failure, known as X-linked adrenal hypoplasia congenita (AHC). A gene isolated from this DSS-AHC critical region was termed *DAX1;* it is a member of the nuclear hormone receptor superfamily[46] and is officially named *NROB1*. In humans, *DAX1* is expressed in the early gonadal ridge and adrenal primordium and is maintained in the fetal adrenal and the adult cortex. Ovarian development was maintained in a woman who had hypogonadotropic hypogonadism associated with a homozygous *DAX1* mutation.[47] The identification of normal male external genitalia in 46,XY individuals with DSS deletion suggests that this locus is not required for testis differentiation. Among about 20 patients with a duplication of Xp21, half had normal female genitalia and a well-documented duplication of the DSS region. Two patients with duplication of DSS showed ambiguous external genitalia.[48]

WNT4 is a member of a large family of Wnt signaling glycoprotein molecules. It is expressed early in the developing mesonephros and hence is also involved in gonadal development. *WNT4* is downregulated in the testis but is maintained in the ovary. Mouse knockout mutants in both sexes fail to develop müllerian ducts. The wolffian ducts are stabilized in the female null mutant because of the differentiation of Leydig-like interstitial cells in the ovary, without virilization of the external genitalia. Therefore, it appears that *WNT4* is normally required for initial müllerian duct development in both sexes but also to prevent Leydig cell differentiation occurring in the ovary.[49] The human *WNT4* gene has been located to chromosome 1p35. A 46,XY female has been described with a duplication of 1p31-p35 in whom *WNT4* was overexpressed.[50] This observation illustrates the role of gene dosage effects in controlling critical steps in the pathway of sex determination.

Mixed Gonadal Dysgenesis

Mixed gonadal dysgenesis (MGD), also termed asymmetric gonadal dysgenesis, is a syndrome of abnormal sexual development that is defined on the basis of gonadal morphologic features: an abnormal testis on one side and a rudimentary gonad, streak, or no gonad at all on the opposite side (Figs. 35-9 and 35-10). Typically, the patients have a 45,X/46,XY karyotype, ambiguous and asymmetric external genitalia, and persistent müllerian duct structures, but a 46,XY karyotype is possible. At birth, the labioscrotal folds are often asymmetric, with a testis palpable unilaterally. Genitography demonstrates the persistence of müllerian structures. Usually, these patients have a uterus, either normal or partly developed, with a fallopian tube on the side of the streak. Development of the genital tract correlates with gonadal differentiation: müllerian ducts are always associated with the streak gonad. Frequently on the other side, depending on the activity of the dysgenetic testis,

Table 35-2 Genes Involved in the Disorders of Sex Development

Gene (Chromosome Location)	Protein	Gonadal Development and Associated Disorders
WT1 (11p13)	Transcription factor	Dysgenetic testis; WAGR, Denys-Drash, and Frasier syndromes
SF1 (9q33)	Nuclear receptor	Dysgenetic testis; adrenal failure
SOX9 (17q24.1)	High-mobility-group transcription factor	Dysgenetic testis or ovotestis; camptomelic dysplasia
SRY (Yp11.3)	High-mobility-group transcription factor	Dysgenetic testis or ovotestis
DHH (12q13.1)	Signaling molecule	Dysgenetic testis; minifascicular neuropathy
ATRX (Xq13.3)	Helicase	Dysgenetic testis; α-thalassemia; mental retardation
DMRT1 (9p24.3)	Transcription factor	Dysgenetic testis; mental retardation
WNT4 (1p35)	Signaling molecule	Dysgenetic testis; mental retardation (duplication)
DAX1 (*NROB1*) (Xp21.3)	Transcriptional regulator, nuclear receptor protein	Dysgenetic testis (duplication); CAH (mutation)
LHCGR (2p21)	G-protein receptor	Leydig cell hypoplasia
DHCR7 (11q12-13)	Enzyme	Smith-Lemli-Opitz syndrome
STAR (8p11.2)	Steroidogenic acute regulatory protein	Male pseudohermaphroditism; lipoid hypertension
CYP11B1 (8q21)	11β-hydroxylase	Female pseudohermaphroditism; CAH
HSD17B3 (9q22)	17β-hydroxysteroid dehydrogenase	Male pseudohermaphroditism; masculinization at puberty
CYP17A1 (10q24.3)	17-hydroxylase/17,20-lyase	Male pseudohermaphroditism; hypertension
CYP21A2 (6q21.3)	21-hydroxylase	Female pseudohermaphroditism; CAH
HSD3B2 (1p13.1)	3β-hydroxysteroid dehydrogenase type II	Male and female pseudohermaphroditism; CAH; elevated DHEA
POR (7q11.2)	Enzyme	Mixed features of 21-hydroxylase and 17,20-lyase deficiency; sometimes associated with Antley-Bixler craniosynostosis
AMHR2 (12q13)	Serine threonine kinase receptor	Persistent müllerian duct syndrome; normal gonadal development
AMH (19p13.3)	Secreted protein	Persistent müllerian duct syndrome; normal gonadal development
SRD5A2 (2p23)	5α-reductase type 2	Male pseudohermaphroditism; masculinization at puberty
AR (Xq11-12)	Androgen receptor, ligand transcription factor	Complete or partial androgen insensitivity syndrome

AMH, anti-müllerian hormone; AMHR2, AMH type II receptor; CAH, congenital adrenal hyperplasia; DHEA, dehydroxyepiandrosterone; POR, cytochrome P450 oxidoreductase; WAGR, *W*ilms' tumor, *a*niridia, *g*enitourinary abnormalities, and mental *r*etardation syndrome.

the suppression of the müllerian ducts is complete or partial and a vas deferens may develop. This testis has been capable of some fetal endocrine function, but histologically it is dysgenetic, with absence of germ cells. Turner stigmata and short stature are found in about half of the cases, in keeping with the chromosomal mosaicism containing an XO cell line.

The presence of a Y chromosome indicates the very likely presence of testicular tissue and predicts the occurrence of virilization at puberty, as well as a high risk of gonadal tumors.[51] The testicular capacity for testosterone secretion may allow normal plasma levels after hCG stimulation and pubertal virilization of patients raised as males.[52] However, although the specific phenotype of subjects bearing a 45,X/46,XY mosaicism is primarily dependent on the chromosomal constitution of the developing gonad, a wide spectrum of phenotypes has been described, from females with clitoral hypertrophy to females with Turner syndrome, to males with hypospadias with or without abnormal internal genitalia or unilateral cryptorchidism, to apparently normal male phenotype.[53-55] MGD may also occur with a 46,XY karyotype in sporadic and familial cases with ambiguous genitalia.[26] In these cases, a low proportion of 45,XO cells may be missed or undetectable by conventional techniques.

Most patients with MGD have been reared as females. For some pediatricians, this is the best choice for patients seen during infancy or at birth, because of the poor growth prognosis and surgical advantages. Repair of the vagina is usually easy, a uterus or hemiuterus is present, and the dysgenetic gonad at high risk of tumor development can be removed early. In patients raised as males or diagnosed late, surgical correction of the hypospadias and the unilateral cryptorchidism is performed, and the testis, if conserved, should be observed regularly to detect the possible development of gonadoblastoma.[52] These individuals virilize at puberty but remain sterile.

Prenatal counseling is very difficult when a 45,X/46,XY mosaicism is diagnosed prenatally, with 90% of the patients having a normal male phenotype.[56,57] There is no correlation between the proportion of the 45,X/46,XY cell lines in the

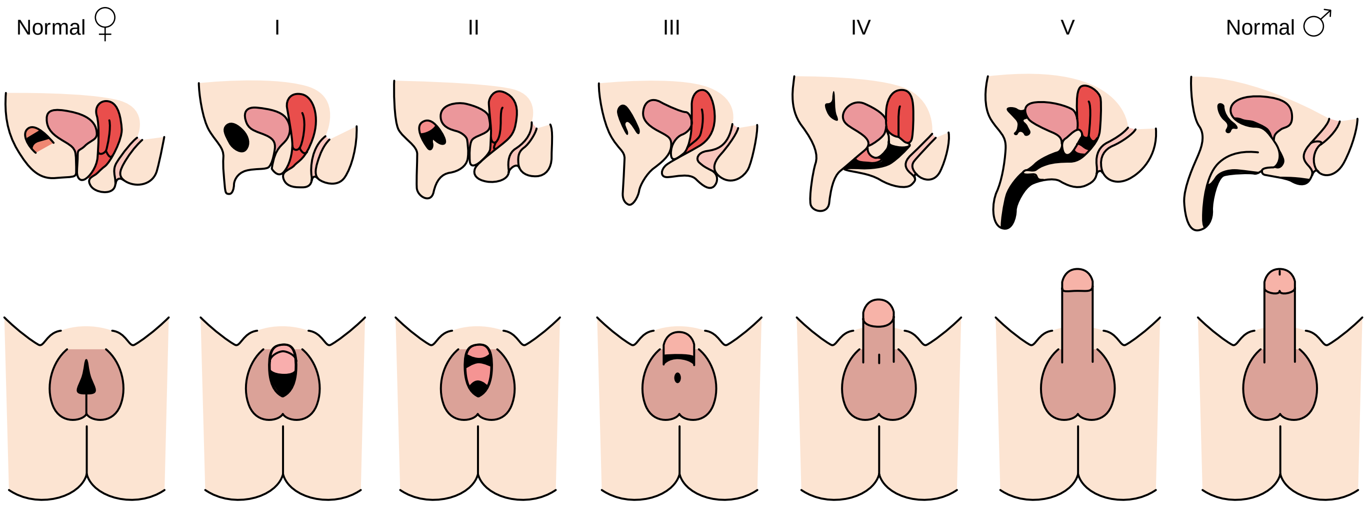

Normal ♀
I
II
III
IV
V
Normal ♂

Figure 35-6 Prader scale, indicating degrees of genital ambiguity.

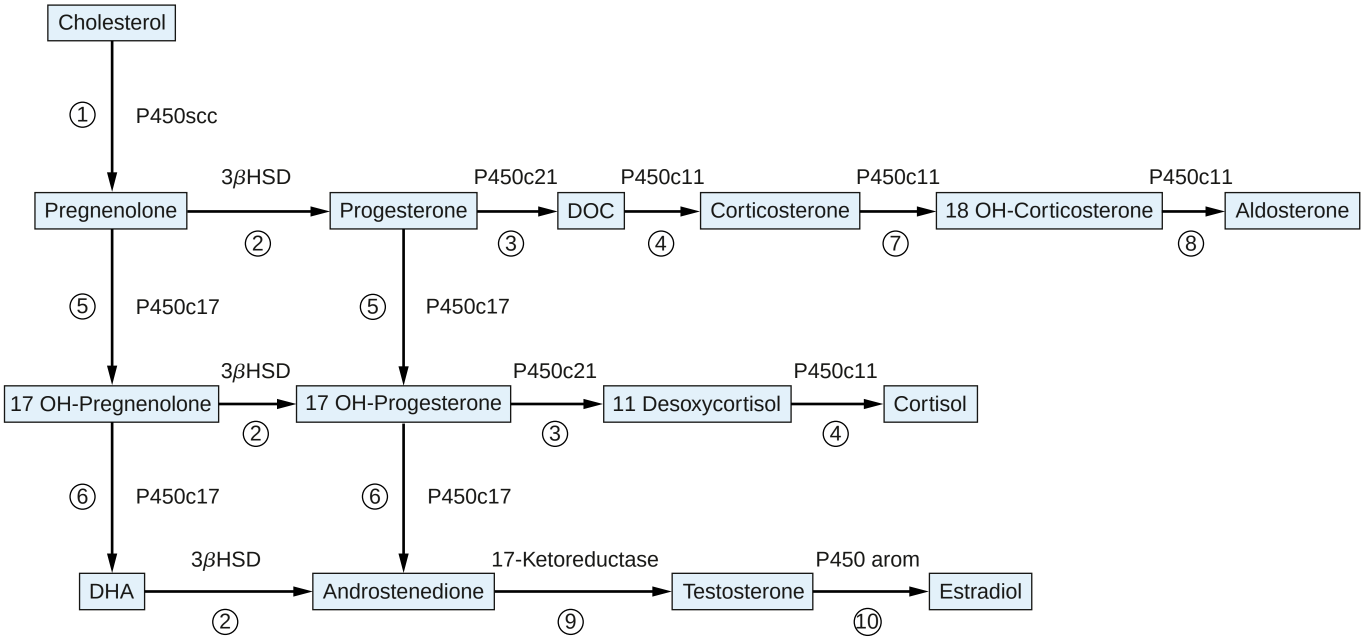

Cholesterol
① P450scc
Pregnenolone
3βHSD ②
Progesterone
P450c21 ③
DOC
P450c11 ④
Corticosterone
P450c11 ⑦
18 OH-Corticosterone
P450c11 ⑧
Aldosterone
⑤ P450c17
⑤ P450c17
17 OH-Pregnenolone
3βHSD ②
17 OH-Progesterone
P450c21 ③
11 Desoxycortisol
P450c11 ④
Cortisol
⑥ P450c17
⑥ P450c17
DHA
3βHSD ②
Androstenedione
17-Ketoreductase ⑨
Testosterone
P450 arom ⑩
Estradiol

Figure 35-7 Flow diagram of steroidogenesis.

blood or in the fibroblasts and phenotype. Therefore, not only does the 10% risk of an abnormal outcome in prenatally diagnosed cases require further attention, but also the outcome of gonadal function in the phenotypic males prenatally diagnosed as having a 45,X/46,XY mosaicism remains to be established.

Testicular Regression Syndrome: Vanishing Testis

The term *testicular regression syndrome* refers to a group of conditions defined by the presence of a 46,XY karyotype and evidence of testicular formation followed by gonadal regression. The pathogenesis of testicular regression remains unknown, and its precise timing is usually unknown. Congenital anorchia, or “vanishing testis,” results from regression of the testes after the critical period of male differentiation.[58,59] These patients have male internal and external genitalia but a complete absence of testicular tissue at birth and no müllerian derivatives. The diagnosis should be considered in all male infants with bilateral cryptorchidism. In the absence of palpable gonads, the critical diagnostic findings are evidence of basal or hCG-stimulated testosterone secretion and AMH above the female range. If some testosterone is produced, it is taken as evidence of some persistent testicular tissue. In agonadal patients, basal gonadotropins are markedly elevated during early infancy or at pubertal age. Further evaluation, eventually including laparotomy or celioscopy and histologic examination of the gonads, could be necessary to make a precise diagnosis.[60,61] These individuals are brought up as males. With testosterone replacement therapy, they have a normal pubertal and sexual life. Implantation of prosthetic testes is recommended for cosmetic reasons and above all for its psychological benefit.[62]

46,XX Males

The condition of 46,XX males is characterized by testicular development in subjects who have two X chromosomes but lack a normal Y chromosome. About 200 cases have been

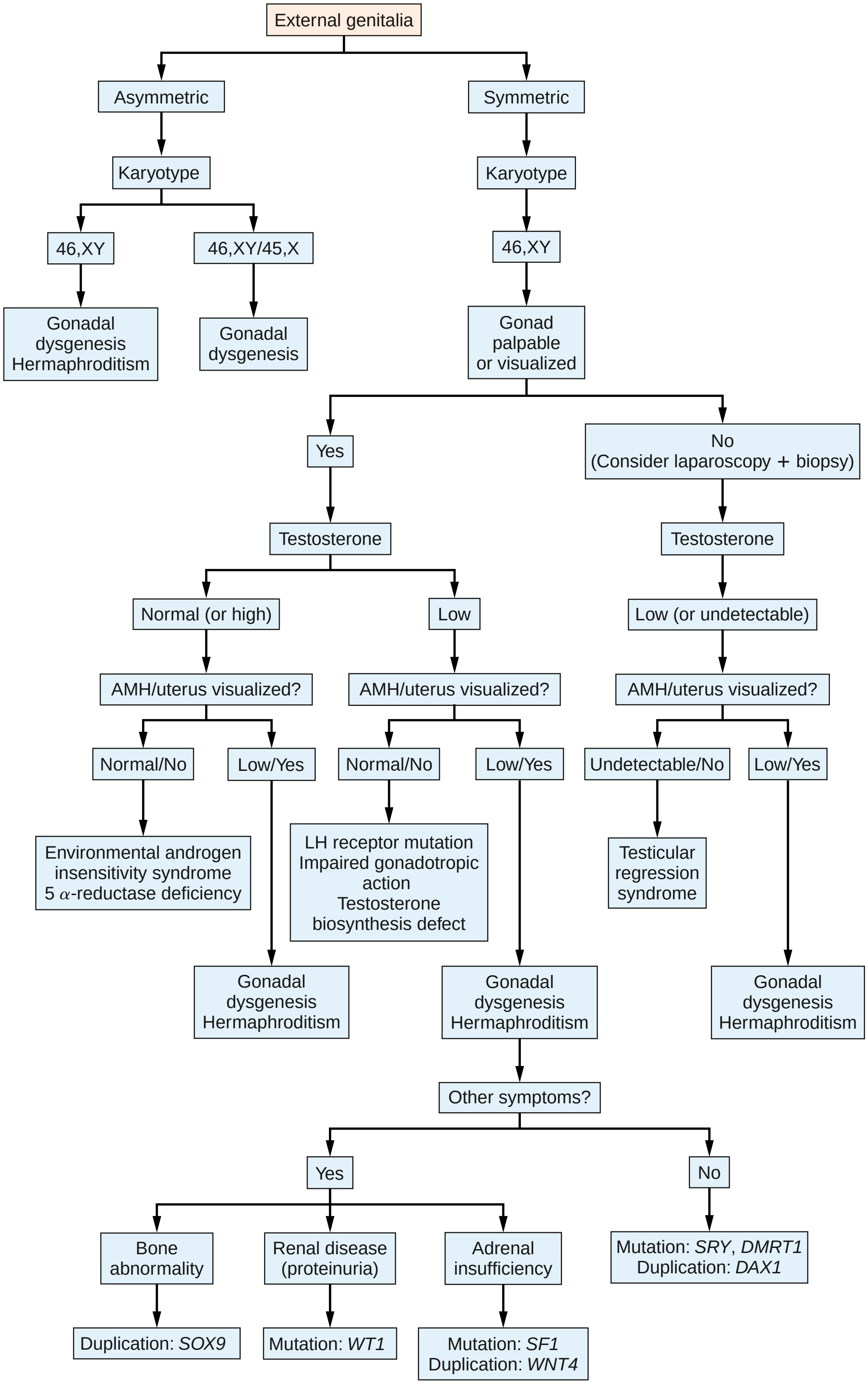

External genitalia
Asymmetric
Symmetric
Karyotype
Karyotype
46,XY
46,XY/45,X
46,XY
Gonadal dysgenesis Hermaphroditism
Gonadal dysgenesis
Gonad palpable or visualized
Yes
No (Consider laparoscopy + biopsy)
Testosterone
Testosterone
Normal (or high)
Low
Low (or undetectable)
AMH/uterus visualized?
AMH/uterus visualized?
AMH/uterus visualized?
Normal/No
Low/Yes
Normal/No
Low/Yes
Undetectable/No
Low/Yes
Environmental androgen insensitivity syndrome 5 α-reductase deficiency
LH receptor mutation Impaired gonadotropic action Testosterone biosynthesis defect
Testicular regression syndrome
Gonadal dysgenesis Hermaphroditism
Gonadal dysgenesis Hermaphroditism
Gonadal dysgenesis Hermaphroditism
Other symptoms?
Yes
No
Bone abnormality
Renal disease (proteinuria)
Adrenal insufficiency
Mutation: SRY, DMRT1 Duplication: DAX1
Duplication: SOX9
Mutation: WT1
Mutation: SF1 Duplication: WNT4

Figure 35-8 Algorithm for etiologic diagnosis in undervirilized male infants. AMH, anti-müllerian hormone; LH, luteinizing hormone.

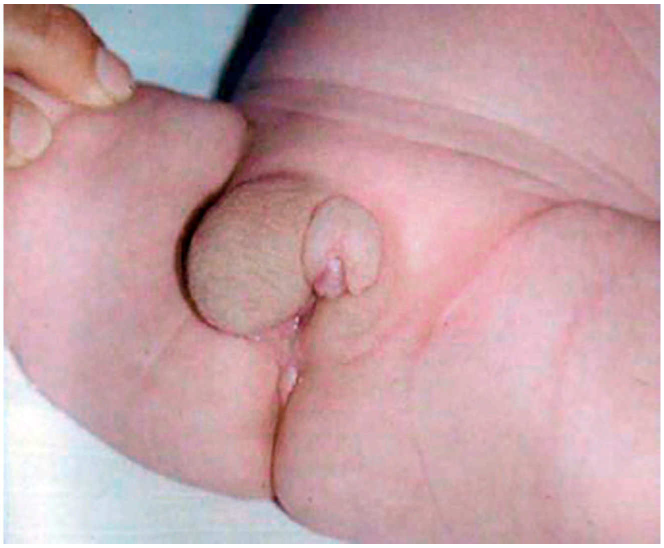


Figure 35-9 Ambiguous genitalia in a 45,X/46,XY infant with mixed gonadal dysgenesis. Note the asymmetric appearance of the scrotum.

reported, but it would appear that 1 of every 20,000 to 30,000 males has a 46,XX karyotype.[63] Most are sporadic cases, but familial cases are reported. Their phenotype varies from normal male to a male with genital ambiguity. At puberty, the patients develop gynecomastia (75%) and some degree of testosterone deficiency with elevated plasma FSH and LH, whereas spermatogenesis is impaired. The testes exhibit the same features as those observed in Klinefelter's syndrome.

Male sex differentiation in these patients results from the transfer of the *SRY* gene by accidental crossing-over (unequal interchange between homologous regions in the short arms of sex chromosomes) during paternal meiosis.[64] XX males may be divided into two subgroups: 46,XX males with the *SRY* gene, 46,XX males without the *SRY* gene. More than 80% of the XX males with normal male phenotype have an *SRY* gene, whereas most of those with genital ambiguity (e.g., micropenis, hypospadias and cryptorchidism, multiple anomalies) have no demonstrable *SRY* sequence.[64,65] The majority of familial cases are *SRY* negative, but the mode of inheritance is unknown, although several modes have been suggested.

Thus, there is genetic as well as phenotypic heterogeneity in 46,XX maleness, indicating that non-Y genes could achieve testicular differentiation. In this respect, some 46,XX males with abnormal external genitalia more closely resemble XX true hermaphrodites, and coexistence of the two conditions in the same family has been reported.[26,66]

Bisexual Gonads: True Hermaphroditism

True hermaphroditism is defined by the presence of both ovarian and testicular tissues, either separately or, more commonly, together as ovotestis. True hermaphroditism is very rare except in Southern Africa, where it is the most common intersex condition.[67] The most frequent presenting symptom before puberty is the abnormal appearance of the external genitalia, with labioscrotal folds and variable degrees of genital ambiguity (Fig. 35-11).[68] However, individuals with normal female phenotype or with almost normal male appearance with penile hypospadias or small penis have been reported, especially in late-diagnosed cases.[69] Undescended gonads and inguinal hernia are frequent. The ovarian tissue is usually normal, contrasting with dysgenetic testicular tissue lacking spermatogonia. The gonadal descent occurs more frequently on the right side. The internal genital differentiation is variable and reflects the gonadal endocrine capabilities. It is often asymmetric. Most, but not all, hermaphrodites have a uterus, which may be fully developed. The nature and location of the gonadal tissue can be bilateral with two ovotestes, lateral with testis on one side and ovary on the other, or unilateral with a normal gonad on one side and an ovotestis on the other side (the most frequent condition).

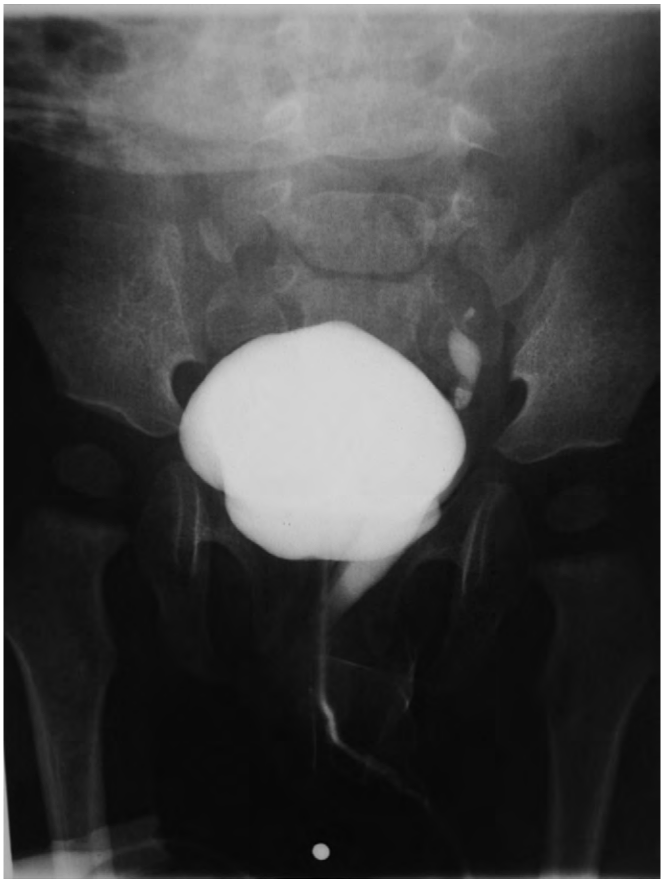


Figure 35-10 Urogenital sinogram in a 45,X/46,XY infant with mixed gonadal dysgenesis.

About 60% of true hermaphrodites have a 46,XX karyotype, and the remainder are characterized by various forms of mosaicism, 46,XX/46,XY.[68] In the majority of 46,XX patients, the search for the *SRY* gene was negative.[70-72] For this reason, it is believed that other unknown mutations on the X chromosome or on an autosome may have impaired normal testicular differentiation.[73] Genetic counseling is still based on the predominance of sporadic cases, because very few familial cases have been reported.[74] The diagnosis of true hermaphroditism should be considered in any patient typically combining ambiguous genitalia, one or no palpable gonad, and 46,XX karyotype. The basal or hCG-stimulated plasma testosterone level is indicative of the presence of Leydig cells. Another important point is the presence of a uterus. Finally, the diagnosis of true hermaphroditism depends on the careful search for ovarian tissue during surgery in an apparently male gonad. The bisexual gonad contains testicular tissue with distinct tubules, and the ovarian tissue has follicles. However, the ovarian tissue must contain oocytes for the diagnosis; the

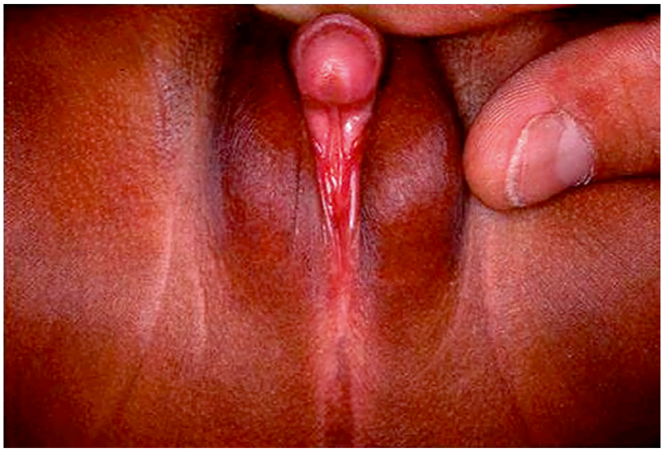


Figure 35-11 Ambiguous genitalia in a 46,XX infant with true hermaphroditism.

presence of only ovarian stroma is not an adequate criterion. With increasing age, ovarian tissue is often normally developed, and pregnancies have been reported.[75] The testicular portion is often immature, and spermatogenesis is rare.[68,76]

The treatment and sex assignment depend on the age at diagnosis. Many patients are referred in the neonatal period. Male sex assignment is considered if there is a good phallic size, correctable hypospadias, and sufficient testicular tissue that could descend into the scrotum. Preservation of testicular tissue should allow normal virilization at puberty, but infertility is constant. Female sex rearing could be discussed if a uterus is present with a vagina, and especially if sufficient ovarian tissue can be preserved.[77] Some patients in whom the ovarian portion of the gonad was preserved have exhibited spontaneous puberty.[73] In these female-reared patients, partial gonadectomy limited to the testicular component must be performed in infancy during reconstructive surgery.[78] Its complete removal is confirmed by the lack of postoperative testosterone secretion. Pregnancy is possible and normal infants have been delivered.[75,79] At adolescence in both cases, the requirement of replacement sex steroid therapy depends on the functional activity of the residual tissue.[80]

Abnormalities in Testicular Differentiation

Leydig Cell Agenesis or Hypoplasia: Luteinizing Hormone Receptor Mutations

During embryogenesis, the effects of hCG are mediated through the hCG/LH receptor, a G protein–coupled receptor, which induces the differentiation of testicular mesenchymal cells into Leydig cells and the subsequent androgen production. *Leydig cell agenesis,* a very rare cause of incomplete testicular differentiation, was first described by Berthezène in its complete form: 46,XY individuals with female external genitalia, lack of breast development, no müllerian derivatives, and primary amenorrhea at puberty.[81] The testes are usually intra-abdominal. The patients secrete no testosterone during hCG stimulation, and plasma LH is elevated. On histologic examination, the gonads are found to be testes with normal Sertoli cells but no mature Leydig cells.

Incomplete forms, termed *Leydig cell hypoplasia,* have been reported. Affected 46,XY individuals present a wide phenotypic spectrum, ranging from complete female external genitalia to males with micropenis. In such cases, partial posterior fusion of the labia and presence of the vas deferens with epididymis is attributed to a partial and transient fetal Leydig cell function.[82-87] Affected 46,XX females have normal female external genitalia, with spontaneous breast development and pubic hair, but may have polycystic ovaries and suffer from amenorrhea or menstrual irregularities. Familial cases have an autosomal recessive inheritance.

The failure of Leydig cells to differentiate normally is caused by a receptor loss-of-function mutation in the LH receptor gene (*LHCGR*). Chromosomal mapping localizes this gene to the chromosome 2p21 loci. Deletion and missense mutations have been described in various alleles of *LHCGR.*

Inborn Error of Cholesterol Biosynthesis: 7-Dehydrocholesterol Reductase Deficiency

Smith-Lemli-Opitz syndrome is an autosomal recessive syndrome characterized by striking craniofacial features, microcephaly, profound mental retardation, severe failure to thrive, growth retardation, syndactyly, and genital malformations.[88] The phenotype is often female in 46,XY affected infants. The sex of rearing depends on the phenotype and surgical repair should be made accordingly.[89]

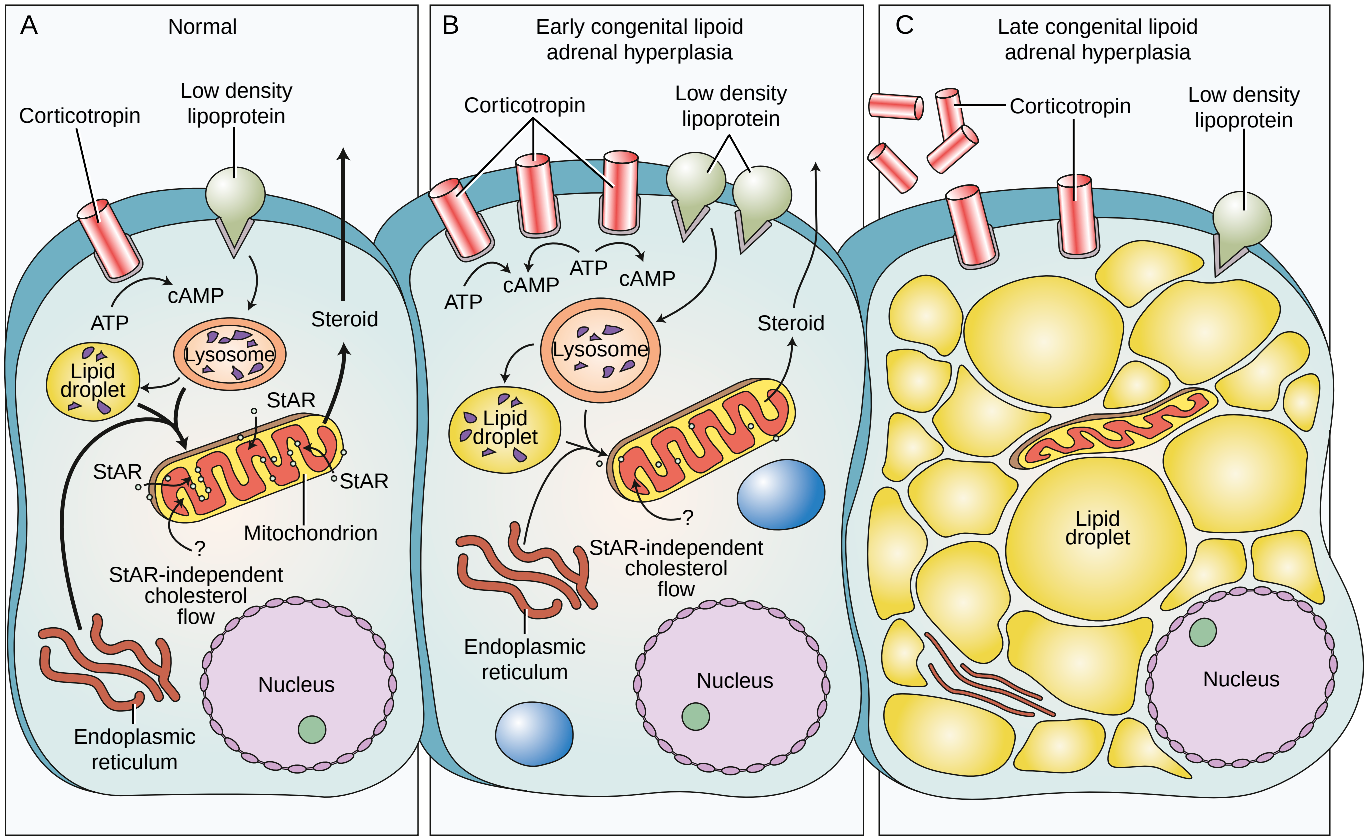
Smith-Lemli-Opitz syndrome is caused by mutations of the human 7-dehydrocholesterol reductase gene (*DHCR7*), which is located on chromosome 11q13. So far, about 20 different mutations have been described.[90] Although it would appear that deficiency of cholesterol, an adrenal hormone precursor, might lead to insufficient synthesis of adrenal and gonadal steroid hormones, the physiopathology of the syndrome is not yet fully elucidated.[91] Diagnosis is based on the finding of low serum cholesterol and high serum 7-dehydrocholesterol levels. Prenatal diagnosis can be made based on high levels of 7-dehydrocholesterol in amniotic fluid.[92-94] Today, diagnosis is confirmed by molecular studies.

Inborn Errors of Testosterone Biosynthesis

Five enzymes are needed for the synthesis of testosterone from cholesterol (see Fig. 35-7).[95] If they are deficient, low testosterone production leads to incomplete male sexual differentiation.[96] The first three enzymes are common to both cortisol and testosterone biosynthetic pathways: 20,22-desmolase or cholesterol side-chain cleavage enzyme, a member of the cytochrome P450 family (P450scc) now designated CYP11A1; 3β-hydroxysteroid dehydrogenase (3β-HSD); and 17α-hydroxylase (P450c17 or CYP17A1). The other two, 17,20-lyase or -desmolase and 17β-hydroxysteroid dehydrogenase/17-ketosteroid reductase (17β-HSD), are obligatory enzymes only in the biosynthesis of C19 steroids. All inborn errors in testosterone biosynthesis are inherited as an autosomal recessive trait. Ambiguity of the external genitalia ranges from complete female phenotype to perineoscrotal hypospadias. The phenotypic heterogeneity relates to the severity of the enzyme defect. Therefore, the identification of the defects in testosterone biosynthesis are based on biochemical findings.

IMPAIRED FORMATION OF PREGNENOLONE: LIPOID CONGENITAL ADRENAL HYPERPLASIA

Lipoid CAH is a rare autosomal recessive disorder in which affected individuals cannot synthesize any steroid hormones (Fig. 35-12); they therefore suffer from severe salt wasting and are often phenotypically female irrespective of the karyotype. The early findings of lipoid hyperplasia of the adrenals suggested that the defect lay in *CYP11A1,* the gene that encodes the enzyme involved in the conversion of cholesterol to pregnenolone. Extensive studies initially failed to identify any abnormality in this gene.[97] Attention was then diverted to the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Nucleus
Endoplasmic reticulum
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Early congenital lipoid adrenal hyperplasia
Corticotropin
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Lipid droplet
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StAR-independent cholesterol flow
Endoplasmic reticulum
Nucleus
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Late congenital lipoid adrenal hyperplasia
Corticotropin
Low density lipoprotein
Lipid droplet
Nucleus

Figure 35-12 Effects of lipoid congenital adrenal hyperplasia in adrenal cells. ATP, adenosine triphosphatase; cAMP, cyclic adenosine monophosphatase; StAR, steroidogenic acute regulatory protein.

steroidogenic acute regulatory (StAR) protein, which mediates the transport of cholesterol from the outer to the inner mitochondrial membrane and thus allows pregnenolone synthesis after trophic stimulation by adrenocorticotropic hormone (ACTH). The encoding gene, *STAR*, was mapped to 8p11.2. About 20 different mutations have been described.[98] In most patients, a severe salt-losing crisis occurs during the first months of life. Sudden deaths have been reported. Affected 46,XX females have normal feminization at puberty and cyclic vaginal bleeding but develop polycystic ovaries.[99,100]

Levels of all steroid hormones are very low to undetectable in blood and do not rise after stimulation with ACTH or hCG. Basal levels of plasma ACTH and renin are very high. In vitro studies performed on either testicular tissue or adrenal or testicular mitochondria have confirmed the incapacity to transform cholesterol into pregnenolone.[98]

The differential diagnosis is CAH. Diagnosis of lipoid CAH is easy in genetic males, because of the association of normal 46,XY karyotype, female or ambiguous phenotype, severe adrenal insufficiency, and lack of response to both ACTH and hCG, but it is difficult in females. The findings of markedly enlarged adrenals and downward displacement of the kidney on ultrasonography, computed tomography, or magnetic resonance imaging are most helpful.[101] In both sexes, LH and FSH levels are markedly elevated at pubertal age, as in agonadal patients.

Lipoid CAH is a very severe disease. With early diagnosis and appropriate glucocorticoid and mineralocorticoid substitutive therapy, survival is possible. Affected males raised as females require gonadectomy and additional estrogen replacement therapy at pubertal age.[102]

3β-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY

3β-HSD converts Δ5-steroids to Δ4-steroids, such as pregnenolone to progesterone, 17-hydroxypregnenolone to 17-hydroxyprogesterone, and dehydroepiandrosterone (DHA) to androstenedione and testosterone (see Fig. 35-7). The conversion occurs in the adrenals, gonads, skin, liver, placenta, and mammary tissues. Impaired 3β-HSD activity affects the production of all classes of steroids, including that of glucocorticoids and mineralocorticoids as well as sex steroid hormones (see Fig. 35-5). Since 1962, many patients of both sexes have been described as having 3β-HSD deficiency, and the heterogeneity of the clinical presentation is evident.[103] Deficient 3β-HSD activity results in male undermasculinization owing to gonadal testosterone deficiency and may also cause slight masculinization (clitoral enlargement and a variable degree of posterior labial fusion) in 46,XX females.[104] This has been attributed to the peripheral conversion of precursors, through extragonadal fetal 3β-HSD. 3β-HSD deficiency also results in cortisol deficiency with salt-wasting or non–salt-wasting CAH.

The pathognomonic biologic finding is increased levels of plasma pregnenolone, 17α-pregnenolone, DHA, and DHAS. Plasma cortisol levels are somewhat reduced or normal but do not rise sufficiently after ACTH stimulation. Plasma ACTH levels are usually high. Paradoxically, plasma levels of Δ^4-androstenedione, 17α-hydroxyprogesterone, and even progesterone might be well above normal. Plasma testosterone is decreased but may be in the low-normal range in adult subjects. The testosterone response to hCG is usually poor in infancy but may be substantial in pubertal boys. Molecular studies report nonsense and frameshift mutations in the type II

3β-HSD gene *(HSD3B2)* of patients with severe salt-losing forms.[105-107] To date, more than 30 mutations have been identified in families with 3β-HSD deficiency.[108,109]

Except for the finding of compound heterozygote mutations in a boy presenting with premature adrenarche, no gene abnormalities have been found so far in partial or late-onset forms of 3β-HSD deficiency. This strongly supports the view that the so-called nonclassic forms of 3β-HSD deficiency do not result from a mutant 3β-HSD isoenzyme.[110]

Management is much the same as for 21-hydroxylase deficiency. It includes administration of glucocorticoids and mineralocorticoids at substitutive doses in the severe forms. At puberty, sex steroid replacement therapy may be needed. The report of a female with 3β-HSD deficiency who had ectopic adrenal tissue in ovaries points out the importance of compliance with treatment.[111]

17α-HYDROXYLASE/17,20-DESMOLASE DEFICIENCY

An essential step in the formation of cortisol and sex steroids is the 17α-hydroxylation of either pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone, respectively (see Fig. 35-7). Both enzyme activities are catalyzed by P450c17, a single enzyme bound to the smooth endoplasmic reticulum. In the human testis, P450c17 is encoded by a single gene, termed *CYP17A1*, which is localized at chromosome 10q24.3.[112]

17α-Hydroxylase deficiency was first reported in a 46,XX female in 1966.[113] The first genotypically male patient was identified 4 years later.[114] Over the next 3 decades, about 150 cases were reported in genetic males and females.[115] In this rare form of CAH, diminished 17α-hydroxylase activity leads to deficient production of both cortisol and sex hormones, resulting in undermasculinization in genetic males and sexual infantilism in genetic females. In both sexes, the other cardinal symptoms are hypertension, hypokalemic alkalosis, and carbohydrate intolerance. Most 46,XY patients have been raised as females because they present with a complete female phenotype and are usually diagnosed at puberty with infantilism. Rarely, the diagnosis is made in infancy, based on hypertension or ambiguous external genitalia.[116] The testes may be intra-abdominal, in the inguinal canal, or in the labioscrotal folds. Inguinal hernias are commonly present. Wolffian derivatives are usually hypoplastic. The onset and natural course of hypertension is variable.

The relative deficiency in cortisol biosynthesis is reflected by a rise in ACTH, which in turn stimulates steroidogenesis up to 17α-hydroxylation. Plasma levels of pregnenolone and progesterone are elevated. There is overproduction of 11-deoxycorticosterone (DOC) and corticosterone (more than 50 to 100 times normal). Plasma testosterone levels are extremely low, with a blunted response to hCG.[117] Plasma FSH and LH concentrations are elevated, as they are in agonadal subjects. The diagnosis should be suspected in cases of male undermasculinization, including 46,XY phenotypic females, who have hyporeninemic hypertension and hypokalemic alkalosis.

The disease is caused by mutation in the *CYP17A1* gene. Molecular genetic studies showed a marked heterogeneity in genetic lesions, including mutations, missense, nonsense, deletions, and insertions.[118-120] To date, about 20 different mutations have been identified, all of them in the coding region. Substitutive treatment is only to replace the deficient glucocorticoid production. It will suppress ACTH overproduction, and thus the overproduction of mineralocorticoids, and improve hypertension. Control of treatment is best performed on clinical parameters.[121] There is no risk of adrenal crisis. Sex steroid replacement therapy is needed at puberty.

There have been only a dozen or so reported cases of male pseudohermaphroditism due to isolated 17,20-desmolase deficiency with normal 17α-hydroxylase activity, evidenced by high levels of 17α-hydroxylated precursors (17α-hydroxypregnenolone and 17α-hydroxyprogesterone) with low androgen production and near-normal cortisol levels. Variable phenotypes are seen, from complete female external genitalia,[122] to severe hypospadias,[122] to normal male phenotype.[122,123] The disorder has also been described in genetic females.[124,125] Cortisol secretion is normal. In plasma, there is an accumulation of progesterone, 17α-hydroxyprogesterone, and, to a variable degree, 17α-hydroxypregnenolone and pregnenolone, whereas the levels of DHA and Δ^4-androstenedione are more or less low. Testosterone and Δ^4-androstenedione do not rise normally after adrenal or gonadal stimulation. The patients do not present any clinical symptom evocative of the disorder other than incomplete virilization in affected males. Diagnosis is established on the basis of systematic hormonal studies. Both ACTH and hCG tests should be performed to bring out the abnormal ratio between C21 and C19 steroids more clearly. Except for surgical repair of the external genitalia and sex steroid substitution therapy at the normal age of puberty, there is no need for other treatment.

17β-HYDROXYSTEROID DEHYDROGENASE 3 DEFICIENCY

The last step in testosterone biosynthesis is the conversion of Δ^4-androstenedione to testosterone, which is performed by an enzyme named 17-ketosteroid reductase(see Fig. 35-7). This is the only reversible step in testosterone biosynthesis, and for this reason the enzyme is also called 17β-hydroxysteroid dehydrogenase (17β-HSD), which describes the conversion of testosterone back to Δ^4-androstenedione. The enzyme also catalyzes the conversion of estrone and estradiol (see Fig. 35-5). In 17β-HSD deficiency, only sex steroid synthesis is altered; adrenal function is normal. The enzymatic defect was identified in about 150 individuals.[126-128]

The enzyme involved in the testicular biosynthesis is the 17β-HSD type 3, which is expressed almost exclusively in the testis and not in the ovary. Abnormalities of *HSD17B3*, the gene encoding 17β–HSD3, lead to 17β–HSD deficiency, which is an autosomal recessive cause of undermasculinization. It is rare within the general population but frequent among a highly inbred Arab population in the Gaza Strip.[128] To date, about 20 different mutations have been defined in affected individuals from different families in western Europe,[127] the United States, Brazil,[129] and the Middle East. The natural history of the disease is remarkable. Deficiency in 17β-HSD gives rise to genetic males with a female phenotype who virilize extensively at puberty. Affected males are often born with female genitalia or a slightly enlarged clitoris.[127,128,130] At puberty, the patients experience rapid and intense virilization, with or without gynecomastia.[126,127] This is believed to occur mainly because of extragonadal peripheral conversion of the high circulating levels of Δ^4-androstenedione and estrone. Most patients are diagnosed at puberty or as adults. The marker of the enzymatic block is the accumulation of Δ^4-androstenedione in blood, with plasma testosterone low or almost normal. Plasma LH is consistently elevated. In infancy, a diagnosis of 17β-HSD deficiency is made only by finding a high ratio of Δ^4-androstenedione to testosterone (≥1) after hCG stimulation.

Because of the almost complete lack of virilization, infants with 17β-HSD deficiency are usually given a female sex assignment at birth. Most often, the diagnosis is made at or after puberty, with the occurrence of severe virilization in a female individual. It has seemed advisable to recommend prepubertal castration and estrogen replacement therapy in this disorder, but management of the disorder has been a matter of controversy.[131] A spontaneous change at puberty to the male gender was observed in several individuals of a large Arab kindred.[132] On this basis, as well as the good response to exogenous testosterone therapy in infancy, the authors proposed to raise all affected genetic males in the male gender. The question whether exposure to high Δ^4-androstenedione levels in utero and postnatally leads to disturbed female gender identity in later life remains largely unsettled, and the best management will be dictated by the age at diagnosis and the familial context.

Impaired Metabolism of Testosterone: 5α-Reductase Deficiency

5α-Reductase deficiency is a rare disorder that was first described as "perineoscrotal hypospadias," because the neonates usually present with a severely hypoplastic penis with the urethra opening on the perineum.[133] It was later established that the disorder results from deficiency of 5α-reductase, the key enzyme in the conversion of testosterone into DHT, the metabolite responsible for normal external masculinization.[133,134] The genitalia are predominantly female, because only testosterone is present (see Fig. 35-4). The disease is inherited as an autosomal recessive trait and has been best described in several Dominican kindreds and in small clusters in some other parts of the world.[135,136]

Different phenotypes can be seen in the same kindred.[137] Typically, the patient presents at birth with a female external phenotype and male internal genital structures. Clitoral enlargement may be present. Most patients are raised as girls. At puberty, they exhibit signs of virilization, with phallic enlargement, descent of the testes, and deepening of the voice without gynecomastia. However, facial and body hair often remain scanty, there is no prostatic tissue, and spermatogenesis is incomplete. At puberty, the plasma basal testosterone-to-DHT ratio is greater than 35. Among children born with ambiguous genitalia, the typical pattern is that of a normal or raised concentration of plasma testosterone with an increased testosterone-to-DHT ratio appearing only after hCG stimulation.[138] However, this parameter may be normal at birth.[139]

Since the identification of the genes *SRD5A1* and *SRD5A2*, which encode, respectively, the two isoenzymes, 5α-reductase types 1 and 2, mutations in *SRD5A2* have been identified in cases of male undermasculinization due to 5α-reductase deficiency. *SRD5A2* is located on chromosome 2p23 and encodes a 254-amino-acid protein.[140,141] About 30 deletions and mutations have been described.[142,143]

Classically, even in subjects born with a clitoris-like penis, bifid scrotum, and severe hypospadias, the penis enlarges at puberty with significant muscular development.[136,144] If the disorder is recognized early, infants can be treated specifically with DHT with a good response.[139] Therefore, if the diagnosis is made during the neonatal period, a male sex of rearing is recommended, and androgen therapy is used to enhance penile growth and facilitate surgical repair of the genitalia. In such patients, further virilization can be expected at puberty, and fertility is theoretically possible. Those diagnosed later in life who have an unambiguous female gender identity should undergo orchiectomy and receive estrogen therapy at the time of puberty. However, there are reports of patients raised as females who underwent reversal of gender role behavior (and married) at adolescence.[145,146] Finally, paternity by intrauterine insemination with sperm from a man with 5α-reductase type 2 deficiency demonstrates that spermatogenesis can occur in this disorder.[147]

Androgen Receptor Defects: Syndromes of Androgen Insensitivity

Testosterone, the primary androgen secreted by the testis, induces the differentiation of the wolffian ducts. Its effects are mediated by an intracellular receptor, AR. The AR gene belongs to a superfamily of ligand-dependent transcription factors and is located at Xq11-12. Receptor or postreceptor defects cause a variety of androgen insensitivity syndromes (AIS). There is a wide range of clinical presentations, from subjects with complete female phenotype to various degrees of undervirilized males.[148] In all instances, the müllerian ducts have normally regressed, a feature that is essential for the diagnosis. In addition to these classic abnormalities of the receptor function, germline mutations in *AR* have been described in a number of diverse conditions, from impaired sperm production and male infertility, to prostate and breast cancer, through to a form of motor neuron disease (Kennedy's disease). More recently, the possibility of somatic *AR* mutations leading to the AIS phenotype has also been raised. An association between the length of the AR polyglutamine tract and the risk of defective spermatogenesis has been reported, as well as with severe forms of hypospadias.

The AR was cloned only in 1988. It has eight exons and encodes a protein with three functional domains: a central domain encoded by exons 2 and 3 involved in the binding of the receptor to chromosomal DNA, a C-terminal domain encoded by exons 4 through 8 that is responsible for the binding of androgen to the receptor, and an N-terminal domain encoded by the large exon 1 that is involved in transcriptional regulation to androgen.

COMPLETE ANDROGEN INSENSITIVITY SYNDROME

The complete androgen insensitivity syndrome (CAIS) was formerly named "testicular feminization." The testosterone secretion is normal, and AMH has induced a normal fetal regression of the müllerian derivatives. Patients come to medical attention during infancy because of inguinal hernia containing a palpable gonad that turns out to be a testis, or at pubertal age as phenotypic girls with primary amenorrhea.[149] At puberty, these patients have a normal female habitus and well-developed breasts; pubic hair is sparse or absent. The vagina is short and blind-ending. The uterus and fallopian tubes are absent. The testes are variably located, either intra-abdominally, inguinally, or in the labia majora. Because of their apparently normal female phenotype, these patients are always reared as girls. They are sterile but in most instances are capable of satisfactory sexual intercourse, with vaginal corrective surgery performed in half of the cases.[150]

The typical hormonal profile, with normal or elevated testosterone levels and high LH levels, is found during the neonatal transient phase of testosterone secretion and at puberty.[151] The molecular basis of the CAIS has been reviewed,[149,152,153] and there is a great heterogeneity in molecular lesions.

The testes are usually removed because of the predisposition to gonadal tumors. There is some controversy among pediatricians as to the best time for castration in patients who are diagnosed in infancy. Estrogen replacement therapy is required at the time of puberty.[154,155]

PARTIAL ANDROGEN INSENSITIVITY SYNDROME

Patients with partial androgen insensitivity syndrome (PAIS) show incomplete fetal masculinization. The phenotype ranges from a predominant male phenotype with severe hypospadias and micropenis to a predominantly female phenotype with clitoromegaly and pubertal gynecomastia (Fig. 35-13). The molecular basis of PAIS has been studied in a large number of patients. The number of mutations described is so large that an

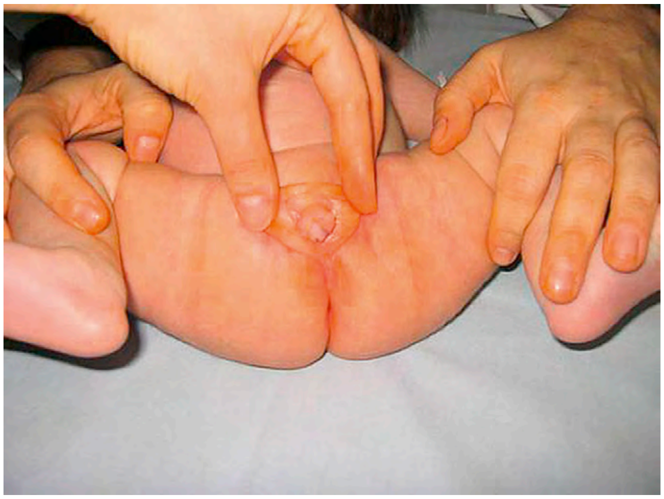

Figure 35-13 Ambiguous genitalia in a 46,XY infant with partial androgen insensitivity syndrome.

AR mutations database has been established and is regularly updated.[156,157] Postzygotic de novo mutations do occur at the expected high rate of an X-linked recessive mutation in PAIS, and somatic mosaicism is of particular clinical relevance for genetic counseling in this disorder. There is no apparent correlation between phenotype and genotype, because the same M780I mutation in exon 6, occurring in the same family, can result in clinical phenotypes characteristic of CAIS or PAIS.[158] Therefore, the molecular defect of the *AR* gene does not alone predict the phenotype in families with AIS.

In sporadic cases, the diagnosis of PAIS remains difficult to assess, and other causes of severe hypospadias with normal AMH must first be ruled out. The diagnosis is likely if both plasma testosterone and LH concentrations are elevated, which can be observed in the first trimester of life and at puberty.[159] Male sex rearing is acceptable only if the penis is significantly responsive to stimulation by intramuscular testosterone, but recent studies showed lack of sexual activity in PAIS adult males.[160,161] Therefore, if PAIS is suspected, it is possible that the best choice remains to rear the child as a female, with reconstructive surgery. Estrogen and progesterone replacement therapy will be necessary at puberty. At present, unless there is an obvious family history with X-linked transmission, the diagnosis of PAIS is still problematic.[161]

Impaired Anti-Müllerian Hormone Production or Action

PERSISTENT MÜLLERIAN DUCT SYNDROME

Persistent müllerian duct syndrome (PMDS) is characterized by the presence of a uterus and fallopian tubes in normally masculinized 46,XY males, often in association with cryptorchidism or inguinal hernia or both. The testes of these patients are usually normal, except for cryptorchidism. The failure of testicular descent most likely results from mechanical restraint by the abdominal müllerian organs. Vasa deferentia are present, as well as epididymides, so that fertility is possible if normal spermatogenesis occurs. Paternity has been recorded.[162] This disease is often familial, presenting as an autosomal recessive trait, an inheritance pattern that correlates with the etiology of the disorder.[163] Although there are only about 150 reports of this condition in the literature, it is possible that this is a gross underestimate, because a number of boys may present with cryptorchidism or inguinal hernia only.

The first step in the process of male differentiation is dependent on AMH produced by Sertoli cells. AMH causes regression of the müllerian ducts that would otherwise, at 8 to 10 weeks' gestation, develop into fallopian tubes, uterus, cervix, and the upper third of the vagina in the female. AMH is a member of the transforming growth factor-β (TGF-β) superfamily and is encoded by a gene containing five exons, located at 19p13.3.[164,165] AMH binds to the type II AMH receptor (AMHR2), a serine/threonine kinase with a single transmembrane domain belonging to the family of type II receptors for TGF-β–related proteins, but requires the presence of the type I AMH receptor for signal transduction. *AMHR2* has been localized to 12q13 and consists of 11 exons; the gene for AMHR1 has not yet been cloned.[166]

PMDS is a genetically transmitted disorder. The phenotype can be produced by a mutation in the gene encoding AMH or by a mutation in the AMH receptor.[167,168] The type of genetic defect may be predicted from the level of serum AMH, which is very low or undetectable in AMH mutations and at the upper limit of normal in AMHR2 mutations. Both types are consistent with an autosomal recessive mode of transmission.

Management involves orchidopexy and hysterectomy. However, the free segment of the spermatic cord is too short, and a partial hysterectomy leaving the cervix intact is recommended to avoid injury to the vasa deferentia embedded in the uterine wall. This procedure allows the descent of the testes after an extensive dissection of the cord to preserve fertility.[163] More recently, it has been suggested that optimal surgical management is orchidopexy, leaving the uterus and fallopian tubes in situ.[169] Meticulous proximal salpingectomy and hysterectomy are indicated only in patients whose müllerian structures limit intrascrotal placement of the testes. The occurrence of testicular cancer has been reported in nine patients with PMDS.[170] Whether the risk for testicular cancer is increased in this disorder or is the same as for cryptorchid patients is still an open question. Thus, orchiectomy has been advised for testes that cannot be mobilized to a palpable location.[169]

Male Pseudohermaphroditism Associated with Malformations

Many syndromes combine dysmorphia and abnormal genitalia, including hypospadias with or without cryptorchidism. The mechanisms of these sex development disorders are unknown. They may involve so-called contiguous gene syndromes because of the gene location on the sex chromosomes or some unknown autosomal control of embryonic development.

Iatrogenic Causes

Considerable attention is given to the possibility that synthetic chemicals (xenobiotics) in the environment may pose a hazard to human reproductive health. The endocrine-disrupting effects of many xenobiotics can be interpreted as interference with the normal regulation of reproductive processes by steroid hormones. A recent review concluded that there is evidence that xenobiotics bind to androgen and estrogen receptors in target tissues, to androgen-binding protein, and to sex hormone-binding globulin.[171] Although environmental chemicals have weak hormonal activity, their ability to interact with more than one steroid-sensitive pathway provides a mechanism by which their hazardous nature can be augmented. A given toxicant may be present in low concentration in the environment and, consequently, harmless by itself. However, numerous potential antagonists working together through several steroid-dependent signaling pathways could prove to be hazardous to normal sex differentiation.[172,173]

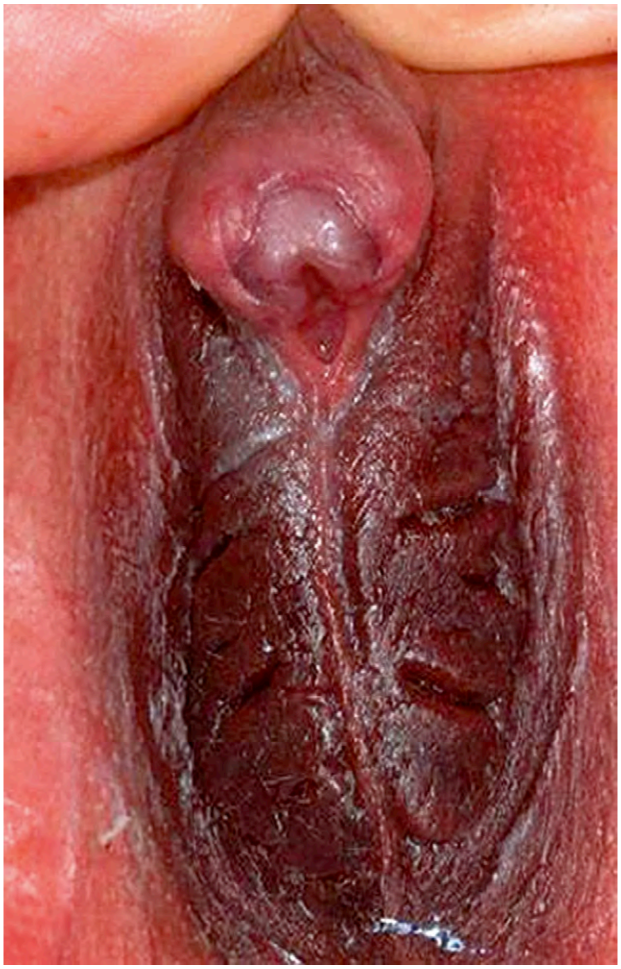

Figure 35-14 Ambiguous genitalia in a 46,XX infant with 21-hydroxylase deficiency.

VIRILIZED FEMALES: SPECIFIC DIAGNOSIS

Excessive Fetal Androgens: Congenital Adrenal Hyperplasia

CAH is a group of autosomal recessive disorders. Adrenal enzyme deficiencies (see Fig. 35-7) are the most frequent causes of female pseudohermaphroditism.

21-Hydroxylase Deficiency

21-Hydroxylase deficiency is the most common variant of CAH, accounting for about 90% of all cases. The clinical syndrome is a consequence of defective 21-hydroxylation of progesterone and 17-OH progesterone, with resulting deficient production of both cortisol and aldosterone and excessive ACTH production (see Fig. 35-7). The disease occurs in a wide spectrum of clinical variants, including a severe form with a defect in aldosterone biosynthesis ("salt-wasting" form), a form with normal aldosterone biosynthesis ("simple virilizing" form) (Fig. 35-14), and a mild "nonclassic" form that may be asymptomatic or may be associated with symptoms of androgen excess developing during childhood or at puberty. In the "classic" (salt-wasting and simple virilizing) forms, signs of androgen excess are often prominent. Salt loss occurs in approximately 80% of cases, whereas virilization of the female fetus is constant. However, the degree of virilization is variable and is usually described according to Prader (see Fig. 35-6). Virilization can be quite important, and even a female fetus with a severe form of the disorder may present with an apparently normal male phenotype except for bilateral cryptorchidism. Some children have moderate virilization at birth, with clitoral enlargement and a partial posterior fusion of the labioscrotal folds. Such infants may be misdiagnosed unless careful genital examination is performed. In the nonclassic forms (late-onset, acquired, cryptic), the affected females are not virilized at birth.

The key measurement for the diagnosis of 21-hydroxylase deficiency is basal plasma 17-hydroxyprogesterone, the steroid above the enzymatic block. In most congenital forms, the elevation is large (30 to 100 ng/mL, 100 to 300 nmol/L). In the nonclassic forms, an ACTH stimulation may be needed. End-test values for 17-hydroxyprogesterone are usually greater than 20 ng/mL (60.5 nmol/L), and in some instances (3%) they are between 12 and 20 ng/mL (36 to 60.5 nmol/L). Even if adequate glucocorticoid and mineralocorticoid replacement therapy is given, unsatisfactory or poor cosmetic results, sexual difficulties, and poor fertility are reported in adult women.[174-176]

During pregnancy, suppression of the overproduction of androgens by the fetal adrenal gland is achieved by giving the mother a daily dose of 20 μg of dexamethasone per kilogram of maternal weight, split in two or three doses.[177,178] However, such treatment should be initiated after careful genetic counseling and monitored by highly specialized teams of pediatric endocrinologists, biologists, and gynecologists.

11β-Hydroxylase Deficiency

11β-Hydroxylase deficiency is the second most frequent cause of CAH (5% to 8% of CAH cases). The inherited deficiency of the 11β-hydroxylase enzyme of the adrenal cortex impairs the conversion of 11-deoxycortisol to cortisol and of deoxycorticosterone to corticosterone and aldosterone (see Fig. 35-7). It usually causes a virilization of the affected female fetus. Patients with the severe, classic form have hypertension, often beginning within the first few years of life, because of overproduction of DOC.[179,180] The hormonal marker of the disorder is the selective elevation of DOC and 11-deoxycortisol (compound S) in plasma. Adrenal crisis is rare because salt loss is not a feature. However, glucocorticoid deficiency can cause hypoglycemia and shock under stress or at the time of initiation of the replacement therapy.

3β-Hydroxysteroid Dehydrogenase Deficiency

3β-HSD deficiency is associated with salt loss and potassium retention. Virilization of the female fetus may occur and is always minimal (clitoral hypertrophy, small labial fusion). In this condition, the association of slightly ambiguous genitalia and the occurrence of a salt-losing syndrome are orienting. The hormonal marker of the disorder is the elevation of pregnenolone and Δ5 precursors in plasma (see Fig.35- 7).

P450 Oxidoreductase Deficiency

P450 oxidoreductase deficiency (PORD) is a newly characterized disorder of adrenal and gonadal steroidogenesis. As such, it can be regarded as a new form of CAH. Patients typically have evidence of adrenal insufficiency (elevated ACTH), partial 17α-hydroxylase deficiency (elevated progesterone), and partial 21-hydroxylase deficiency (elevated 17-hydroxyprogesterone). Many patients were born to mothers who became virilized during their pregnancy, reflecting partially deficient aromatase activity. Cytoplasmic forms of cytochrome P450 that require electron donation by P450 oxidoreductase (POR) catalyze all of these activities. Most of the patients with PORD in published reports have also had the Antley-Bixler skeletal malformation syndrome.[181]

Transplacental Passage of Androgens

Excessive Placental Androgens: P450 Aromatase Deficiency

Aromatase catalyzes the conversion of androgens to estrogens in many tissues and is localized in the placenta, the ovary or testes, and a variety of extragonadal tissues. It plays a key role in the control of reproductive function by regulating the production of estrogens.

Human aromatase deficiency is a rare autosomal hereditary disease and is usually caused by single base-pair changes resulting in amino acid substitution or premature stop codons in the *CYP19A1* gene.[182] In most cases, the affected mother presents with virilization in the third trimester of pregnancy.[183-187] Affected female newborns have clitoromegaly because of the failure of conversion of fetal dehydroepiandrosterone to estrogen in the placenta and subsequent conversion to androgens in the periphery. If the disorder is suspected from the occurrence of marked virilization in the mother, the diagnosis relies on the measurement of androgens (excessively high) and estrogens (extremely low or immeasurable) in the pregnant mother before delivery. After delivery, the diagnosis is made by further hormonal studies in the child: they are normal after day 2 in a quite virilized girl. Diagnosis is then made on the basis of molecular studies.[185-187]

Excessive Maternal Androgens

Masculinization of the external genitalia can occur if a female fetus is exposed to maternally produced androgens crossing the placenta. Internal genitalia are normal. This disorder concerns female offspring of mothers with CAH,[188] adrenal tumors,[189] ovarian tumors,[190] or rare hCG-dependent luteoma of pregnancy. Investigation of abnormal androgen production by the mother must be performed immediately after delivery.[191]

Female Pseudohermaphroditism Associated with Malformations

A number of birth defects include enlargement of the clitoris in genetic females. However, these are non-androgen–dependent causes of female pseudohermaphroditism. Genital abnormalities are frequently associated with imperforate anus, renal agenesis, and other congenital malformations of the intestine and the urinary tract.[192,193] In contrast to the androgen-induced forms of female pseudohermaphroditism, the internal genitalia may also be malformed, and persistence of a cloaca is not exceptional. In all of these cases, the only treatment is surgical repair of the external genitalia.

CONCLUSION

There are medical and surgical criteria used to assign gender in a child with ambiguous genitalia. In the case of 46,XX CAH or 46,XY CAIS, the decision is easier, and the female gender is chosen by most. Among patients with ambiguous presentations, the most difficult discussions concern those who are poor androgen responders. In these cases, the choice of gender rests on the penile size, the response of the penis to androgen stimulation, and the presence of müllerian derivatives. Challenging the genital tubercle with androgens could be useful but does not give evidence that responders during the neonatal period will remain so after puberty.

Anatomic features should allow definition of the potential capacity of penetrative sexual intercourse. The potential fertility of the patient may influence the decision of gender. Also to be taken into consideration are the disappointing and controversial outcomes of genital reconstructive surgery. Clitoral sensitivity has been reported to be affected in genitoplasty, and early vaginal reconstruction requires revision at puberty in most cases, leading some surgeons to defer these reconstructions to a later stage of life.[194] Genital and especially clitoral surgery is often associated with difficulties in adult sexual function, even with newer, nerve-sparing techniques.

The way the situation is presented to the parents in the first few days of life and their understanding of the dilemmas may forge parental insight. The parents' instinctive perception in the final decision is strongly determined by the social and cultural environment, the sex being commonly considered as an instrument of reproduction and pleasure as well as a main identifier for society. Finally, the main paradox is that the only person who is not party to the decision in the neonatal period is the patient. This probably explains the controversies raised by various patient support groups on behalf of those who considered that their sex was imposed upon them. For the medical team, the difficulty of the choice of gender is "how to make the least bad choice."

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 36

SURGICAL MANAGEMENT OF FEMALE GENITAL ANOMALIES, DISORDERS OF SEXUAL DEVELOPMENT, UROGENITAL SINUS, AND CLOACAL ANOMALIES

Elizabeth B. Yerkes and Richard C. Rink

Normal development of the female internal and external genitalia occurs in an orderly sequence of events. Failure of development of the appropriate precursors or interruption of the normal sequence of events may occur during early embryologic development. The resultant anomalies range from imperceptible or clinically inconsequential abnormalities to complete absence or severe malformation of the genital tract. Other abnormalities are acquired or have a delayed clinical presentation. The complexity of surgical intervention follows a similar spectrum and can be very demanding technically.

This chapter describes the initial assessment, surgical management and outcomes, for these abnormalities of the internal and external genitalia. Although many of the more severe anomalies result in some degree of genital ambiguity, we discuss only female genital reconstruction and the related current controversies and opinions. Genital surgery in males is discussed in Chapters 41, 42, and 43. The most complex female anomalies involve the genital, urinary, and gastrointestinal systems; the surgical management and outcomes for these children are discussed here.

ABNORMALITIES OF THE EXTERNAL GENITALIA

Evaluation and treatment of abnormalities of the external genitalia of female children and adolescents typically fall in the domain of general and pediatric urologists. Many academic medical communities enjoy multispecialty collaboration in the care of infants and teenagers with the most complex anomalies of the genitourinary tract. Symptomatic lesions are brought to the attention of the primary care provider, but many abnormalities are first noted during a diaper change or on routine examination. Minor variations of "normal" are common and require only reassurance. On initial inspection, other congenital or acquired anomalies of the labia or of the structures between the labia *(interlabial abnormalities)* may be alarming. However, familiarity with the normal anatomic landmarks typically leads to the correct diagnosis.

Any productive examination of the external genitalia should begin by gaining the confidence of the parent and child. Gentle outward and lateral traction on the labia majora should expose the mucosal lining of the labia minora, which form a partial hood over the clitoris. The urethral meatus is visible just anterior to the vaginal introitus. Outward traction on the labia majora also allows inspection of the distal vaginal vault by atraumatically tenting the hymen and allowing the anterior and posterior vaginal walls to part. Placing the child in a knee-to-chest prone position with the buttocks elevated has a similar effect. "Floating" the hymen with a few drops of saline may demonstrate the anatomy better.[1] The absence of gonads within the labia majora is confirmed.

There are a number of normal variants of virginal hymenal tissue (Fig. 36-1), and recognition of these variants is particularly important when investigating cases of potential sexual abuse. Hymenal tissue in the newborn may be thickened and protuberant due to the effects of maternal estrogens, and these changes may persist for up to 2 years.[2] Bumps and notches on the anterior rim of the hymen are observed in normal prepubertal girls, and nonspecific inflammatory changes or vascularity is common. A normal genital examination is the most common finding in a child who has experienced sexual abuse. There are a number of indeterminate findings, such as notching or clefts between 4 and 8 o'clock, smooth but thinned (1 mm) posterior hymenal rim, and marked immediate anal dilation greater than 2 cm. Thickening or scarring along the posterior rim is suspicious, but only bruising or complete transection of the hymen posteriorly confirms trauma.[1]

Labial Abnormalities

Because of the influences of maternal estrogens, newborns often have significant labial edema and may have vaginal discharge or withdrawal bleeding. These changes typically subside by 2 months of age as the hormonal milieu normalizes. After the neonatal period, the appearance of the labia is fairly consistent until adolescence.[2] Occasional asymmetry or discoloration may occur but is rarely of consequence. An inguinal defect, such as a hernia or gonad, should be considered in the differential diagnosis of a unilateral labial mass. Labial lipomas and hemangiomas occur uncommonly in childhood. Labial hemangiomas usually regress at puberty, and intermittent bleeding responds to compression or silver nitrate cauterization. Labial varices are likewise best managed expectantly unless bleeding occurs. Labial cysts are rare in the prepubertal child, and symptomatic posterior vestibular cysts can be incised.[3]

A variety of dermatologic disorders and infectious lesions can involve the labia. Dermatitis, candidiasis, and eczema affect the labia and should be managed with topical agents. Chickenpox may extensively involve the vulvar region, and topical antibiotic ointment helps prevent superinfection. Vitiligo is a patchy, congenital absence of pigment, but disorders such as lichen sclerosus can also result in depigmentation. Lichen sclerosus and erosive chronic dermatologic conditions can lead to deviation of the urinary stream, painful paraphimosis, or infection from fusion of the minor labial folds over the clitoris and urethral meatus. Judicious surgical release may be required.[3]

Labial Adhesions or Labial Agglutination

Adhesion or agglutination of the labia minora in children occurs as a result of vulvar irritation. Trauma, superficial infection, and chemical irritation from perineal wetness have been implicated. Denudation of the delicate, poorly estrogenized labial epithelium allows subsequent agglutination.

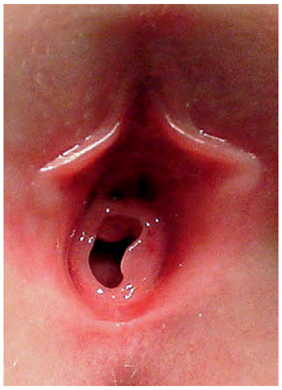

Figure 36-1 Normal hymenal variant: Annular with bump. Crescentic and redundant are other normal variants.

Labial adhesions are most commonly discovered incidentally in infancy or early childhood; newborns seem to be spared by the influence of maternal estrogen. Adhesion begins in the posterior fourchette and progresses anteriorly, forming an almost translucent midline raphe (Fig. 36-2). The vaginal introitus and urethral meatus may be completely hidden by the adhesions.[4]

Labial adhesions are typically asymptomatic. Symptoms suggestive of urinary tract infection may occasionally occur if adhesions deflect or block the normal efflux of urine. Trapping of urine behind the adhesions makes it impossible to obtain a valid voided specimen, making the diagnosis of actual urinary infection problematic. Pruritus and postvoid dribbling can also occur secondary to trapped urine, and dampness may be minimized by blotting inward with more tissue after wiping.

The majority of labial adhesions resolve spontaneously during hormonal changes at puberty. In general, labial adhesions do not warrant treatment. Symptomatic or otherwise bothersome adhesions can be successfully separated with the application of estrogen cream (Premarin 0.625 mg/g) twice daily for 1 to 2 weeks. Use of a cotton swab to apply the cream with gentle pressure along the line of adhesion increases the success of treatment. Temporary hyperpigmentation of the labia may occur during treatment. Prolonged courses of estrogen should be avoided. Incomplete separation is acceptable as long as the symptoms resolve. Adhesions that have thinned but not parted can be gently separated with lubricated swab after the application of a topical anesthetic cream. Forceful separation is painful and traumatic for the child.

True labial fusion can result from severe chronic vulvar inflammation, and adhesions that fail to thin with estrogen therapy may need to be surgically separated. Regardless of the method of separation, routine application of a bland ointment to the previously attached tissues minimizes the risk of readhesion. Management of constipation is also beneficial.

Although almost all adhesions are believed to result from benign inflammation of the vulvar tissues, labial adhesions have also been linked to sexual abuse. In general, the adhesions related to injury are more dense, as are those created by repeated manual separation in the office. Posterior fourchette scars that deviate off midline and neovascularity that does not cross the midline are other findings of concern. The discovery of routine labial adhesions should not raise concern for abuse, but vulvar changes in combination with other signs or symptoms of abuse warrant further investigation.[5]

Complete labial fusion, without an apparent thin midline membrane, results in a single anterior orifice that suggests a *urogenital sinus* (UGS) abnormality. UGS anomalies are typically associated with *disorders of sex development* and are discussed later in this chapter.

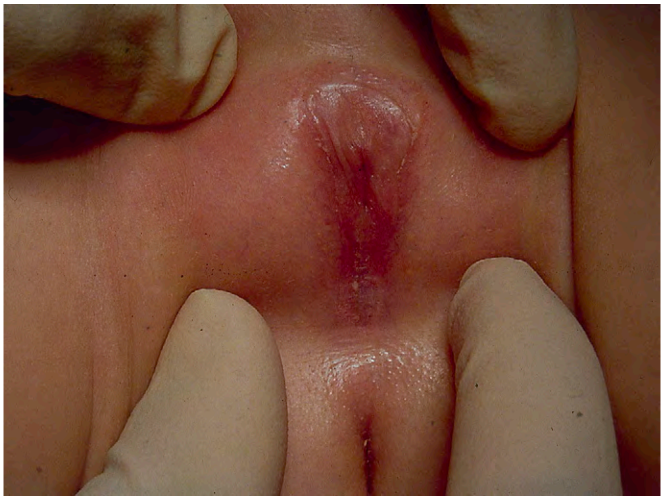

Figure 36-2 Labial adhesions.

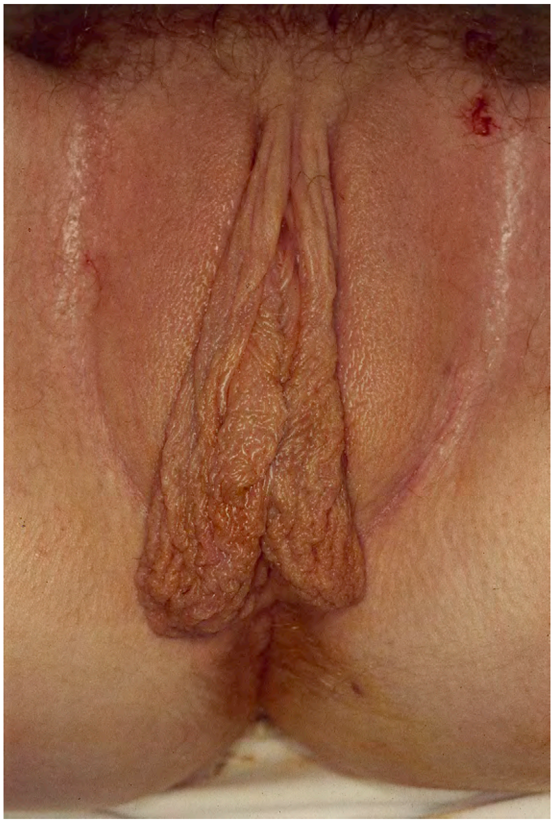

Figure 36-3 Labial hypertrophy.

Labial Hypertrophy

Isolated prominence of the labia minora occasionally occurs and is likely a normal variant (Fig. 36-3). No clear etiology has been identified. In general, elongation of the labia is asymptomatic, but irritation of the exposed tissue by chronic minor

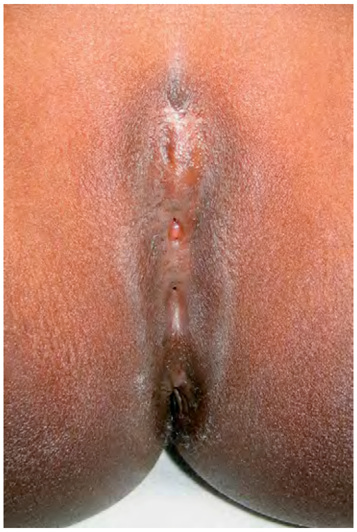

Figure 36-4 Female genital cutting, type III. (Courtesy of Dr. Aseem Shukla.)

trauma (walking and sitting) may occur. Good hygiene and the avoidance of tight clothing are helpful. Surgical reduction or wedge resection can be performed if the patient requests revision.[2,6,7]

Female Genital Cutting

Female genital cutting (FGC), the current preferred term in the international community for the practice also known as female circumcision or female genital mutilation, is practiced in countries throughout the Middle East and Africa and in some Muslim societies of Southeast Asia. Amnesty International estimates that 130 million women have undergone some form of FGC, with at least 2 million procedures performed annually.[8]

Although trained professionals perform FGC with a local anesthetic, FGC is also practiced by women in the bush without anesthesia or aseptic conditions. The procedure is a culturally based, ritualistic initiation into adult society performed anytime between infancy and puberty. In some societies, it is viewed as a religious requirement for the preservation of chastity and for ensuring future social acceptance.[9] The World Health Organization (WHO) divides the practice of FGC or cutting into four types. Type I FGC involves removal or splitting of the clitoral hood with or without excision of the clitoris. Type II FGC involves excision of the clitoris with partial or total excision of the labia minora. Type III FGC involves excision of part or all of the external genitalia and stitching or narrowing of the vaginal opening *(infibulation)* (Fig. 36-4). Type IV is a collection of practices that may not involve removal of tissue. The genitalia may be pricked, burned, or scarred; the vagina may be ripped to cause narrowing.[10]

Infibulation, or *pharaonic circumcision* with excision of the clitoris, labia minora, and two thirds of the labia majora, is the most dramatic procedure and that associated with the most short- and long-term complications. The raw vulvar edges are reapproximated with suture or twigs, leaving a small posterior hole for efflux of urine and menses. Acute complications include hemorrhage, infection, and urinary retention. Dense scars, gynecologic infections, inclusion cysts, and retained menses may develop. Hygiene can be a significant problem with the slow trickle of urine and blood, and chronic urinary or uterine infections may result.[9] Despite cultural pressure to deny sexual desire, women who have undergone FGC describe orgasm and happy marriage.[11] Some degree of deinfibulation is performed at the time of marriage, but the vulva must be opened urgently to allow delivery of a child. At least partial reinfibulation is performed.[9] A 2006 WHO collaborative study confirmed increased infant deaths and adverse obstetric outcomes, such as cesarean section and postpartum hemorrhage, for women who had undergone type I, II, or III FGC.[12]

As immigration from these regions increases, the prevalence of affected females in Western nations may rise. Physicians may encounter complications of infibulation or be asked to perform this form of genital modification. The WHO, the American Medical Association, and other organizations have issued statements condemning the participation of physicians in medically unnecessary genital modification. Infibulation and postpartum reinfibulation are illegal by an Act of Parliament in the United Kingdom; no such national legislation exists in the United States.[13,14] In 2006, the U.S. state of Georgia proposed a law prohibiting FGC after a father was prosecuted for personally removing his daughter's clitoris.[8] Although procedures that may endanger the health of women are not to be condoned, cultural awareness and sensitivity are obviously very important in the care of these women and children.[13] Education of men and women about the associated health risks is obligatory.

Clitoral Abnormalities

The discovery of an enlarged clitoris *(clitoromegaly)* in a newborn girl warrants thorough investigation for potentially life-threatening conditions. A clinical impression may be confirmed by calculation of the clitoral index, as described by Huffman.[15] The clitoral index is determined by multiplying the width of the glans times the length of the phallus; it is thought to be normal if less than 4.35 mm and worrisome if greater than 10 mm. In premature infants, a developmentally appropriate clitoris can appear relatively exposed and large.[2] Maternal estrogens have less effect on the labial tissues, so there is less prenatal labial fat deposition to conceal the clitoris. This disproportion improves as the child matures. Clitoromegaly is most commonly related to in utero androgen exposure. Neurofibromatosis, hemangioma, lymphangioma, and chronic vulvar irritation are less common causes of clitoral enlargement.[6]

Complete agenesis of the clitoris is rare. A bifid or duplicated clitoris is found in females with the exstrophy-epispadias complex. Because of the separation of the clitoral halves, the labia minora and labia majora also part in the midline, leaving an anterior cleft. Approximation of the bifid clitoris, labioplasty, and monsplasty constitute one aspect of the complex genitourinary reconstruction in exstrophy-epispadias (see Chapter 30).

Interlabial Masses

Identification of a mass between the labia majora can be quite concerning for a parent, but most of these uncommon lesions are benign. The lesions emanate from the urethra or vagina and may be large enough to eclipse the normal interlabial landmarks. Careful inspection of the position and appearance of the mass, in combination with consideration of the age, ethnicity, and symptoms of the patient, helps confirm the diagnosis in most instances. Radiographic evaluation is not necessary in most cases, although abdominal and pelvic ultrasonography may be helpful if the diagnosis remains unclear.[16] Urethral catheterization and endoscopy are rarely required for diagnosis.

Paraurethral Cyst

Congenital paraurethral cysts are the uncommon result of ductal obstruction of the Skene paraurethral gland. The cyst is typically based on the inferolateral aspect of the distal urethra and may result in eccentric displacement of the urethral meatus. Very large lesions can cause spraying of the urinary stream or eversion of the anterior vaginal wall. Paraurethral cysts are smooth, soft, and whitish; small, superficial vessels may be present (Fig. 36-5A). Usually, cysts identified in newborns spontaneously drain within several months, but aspiration or incision with a small needle is occasionally required

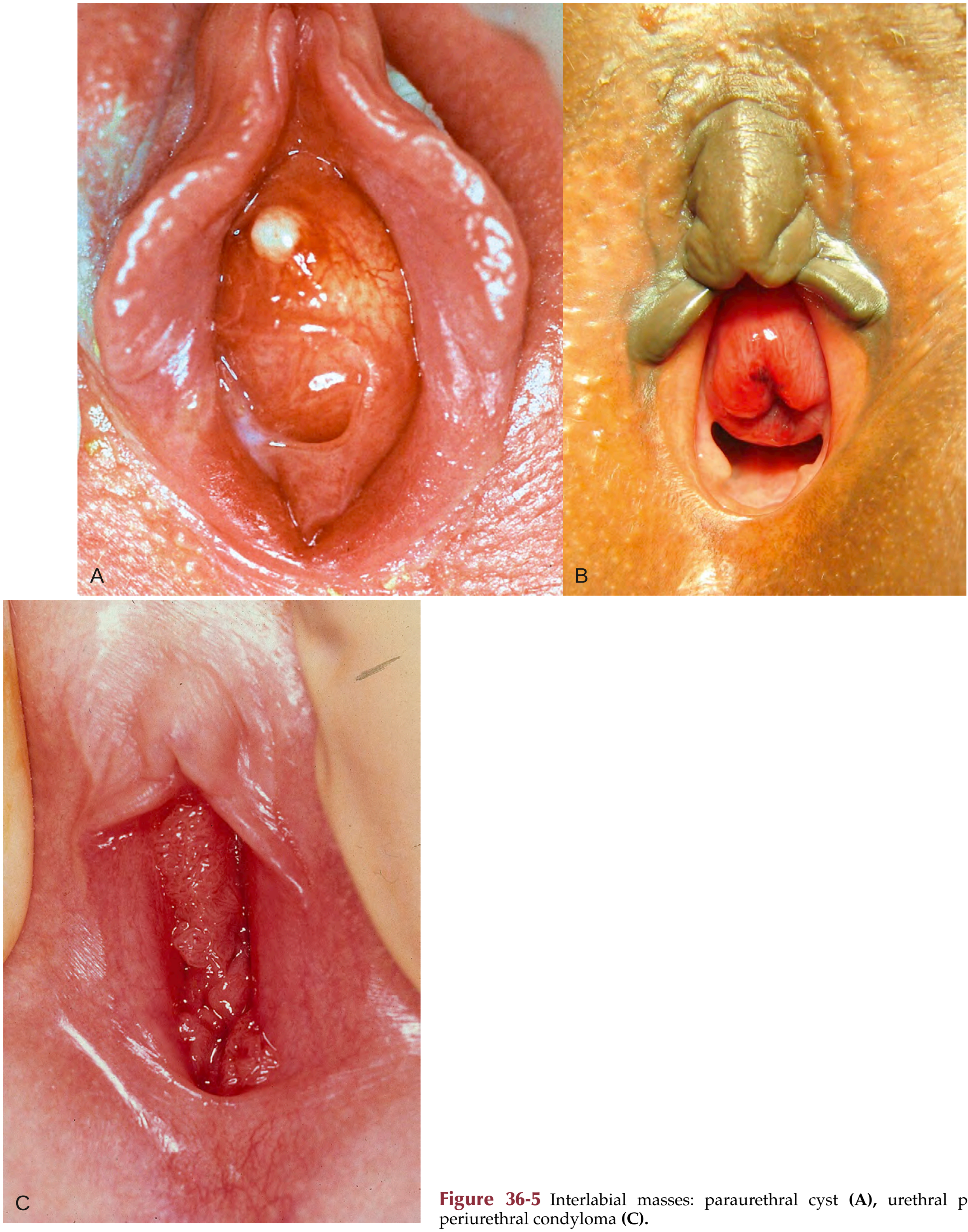

Figure 36-5 Interlabial masses: paraurethral cyst **(A),** urethral prolapse **(B),** periurethral condyloma **(C).**

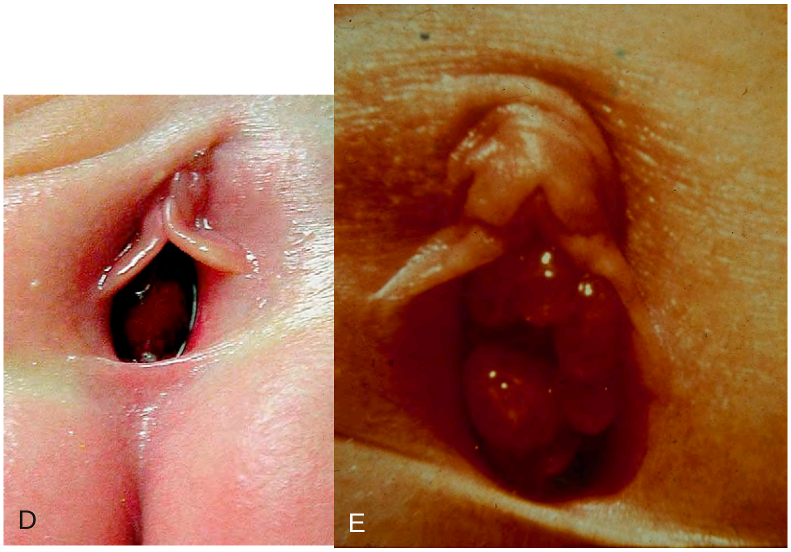

Figure 36-5, cont'd. Prolapsed ureterocele **(D),** and sarcoma botryoides **(E)**. (**E,** From Yerkes E, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol.* 2002;14:12-30. Copyright 2002, Medical Economics.)

for decompression. Aspiration of the mucoid fluid results in complete decompression without recurrence. The cyst wall is lined with stratified squamous or transitional epithelium.[17]

Urethral Prolapse

Prolapse or eversion of the distal urethral mucosa occurs most commonly in prepubertal black females at a mean age of 5.4 years.[18] Bloody spotting is the most frequent presentation,[18-20] and perineal fullness or discomfort may occur as well. Dysuria, frequency, retention, or other urinary symptoms have been reported in up to half of the cases.[19,20] The cause is uncertain, although abnormal urethral muscular attachments, hypoestrogenized tissues, and trauma have been implicated.[21] Thorough questioning often reveals a history of coughing, constipation, or abdominal straining.[20,21]

The prolapse may be circumferential or partial, with partial eversion typically involving the posterior urethral wall.[20] Except in the most acute cases, the urethral mucosa is congested and friable and forms a beefy-red or purple doughnut around the urethral meatus (see Fig. 36-5B). The prolapsed tissue may be significant enough to fill the introitus, but retraction of the labia should allow visualization of the hymen. If necessary, urethral intubation may be performed for confirmation.

The symptoms and the prolapse itself may resolve with sitz baths and a trial of topical estrogen cream, but incomplete resolution or recurrent prolapse is common.[18,21] Excision of the prolapsed mucosa by quadrants, with approximation of the mucosal edges, is the most definitive management. Surgical therapy is indicated in the event of thrombosis and necrosis, recurrent prolapse, failure of medical therapy, or significant symptoms. A Foley catheter may be left in place overnight as a convenience for the patient. Amputation of the prolapsed tissue by ligation over a Foley catheter is not recommended.

Condylomata Acuminata (Human Papillomavirus)

Verrucous condylomatous lesions of the vulva or perianal region in children are most commonly associated with human papillomavirus (HPV) types 6 and 11. Fleshy masses at the urethral meatus or vaginal introitus also occur (see Fig. 36-5C). Although the incubation period for HPV is typically 4 to 6 weeks, lesions may take several months to become evident. Perinatal HPV transmission to an infant is common, yet the mode of transmission (cervicovaginal, amniotic, hematologic) is not well understood. Although lesions detected up to 2 years of age may have been acquired perinatally, any genital or perianal condyloma in a child warrants consideration of sexual abuse.[22] Genital warts may also occur by autoinoculation or heteroinoculation. Condyloma is found in only 2% of sexually abused children, but up to 43% of children with condyloma have been found to have a history of sexual contact.[23,24]

Treatment of condyloma in children is best approached with the patient under general anesthesia, to allow excisional biopsy for viral typing before carbon dioxide laser vaporization. Intraoperative application of 5% acetic acid helps highlight the lesions. Sitz baths and oral analgesics are appropriate for pain relief, and a topical antibiotic ointment should be applied several times daily.[22]

Urethral Polyp

Polyps of the female posterior urethra are a rare type of interlabial mass. Blood spotting may be associated with a polyp that protrudes through the urethral meatus. Excision with fulguration of the base is adequate management.[25]

Bladder Prolapse

Prolapse of the posterior bladder wall through a patulous bladder neck is seen uncommonly in female patients with exstrophy-epispadias. Congestion or ischemia of the mucosa and ureteral obstruction are the greatest concerns. Manual reduction is possible, but earlier definitive surgical correction may be required.

Imperforate Hymen

Imperforate hymen results from failure of distal canalization of the vaginal plate at the junction between the UGS and the vagina. The abnormality is usually identified in the newborn period or during the course of investigation of primary amenorrhea. Under the influence of maternal estrogens, the newborn produces vaginal and cervical secretions. In the setting of imperforate hymen, efflux of these secretions is not permitted, and the newborn may present with a whitish bulging mass filling the introitus (*hydrocolpos* or *mucocolpos*). The vagina is quite distensible and may contain up to a liter of mucous secretions.[6] Secondary obstruction of the upper urinary tract can result from vaginal distention. Bedside incision of the tense hymen allows drainage of the retained secretions. Although the upper tracts generally decompress after incision of the hymen, this should be confirmed by repeat ultrasonography. If imperforate hymen is missed during the neonatal period, it may be discovered after the onset of puberty as a bluish, bulging introital mass. Microperforations and hymenal bands are relatively common and may be addressed before puberty.

Prolapsed Ureterocele

Large ectopic ureteroceles typically are associated with the upper pole of a duplex system and occasionally manifest as an interlabial mass with prolapse of the ureterocele through the urethra. Caldamone and associates[26] reported an 11% incidence of prolapse, predominantly in white females. Although ureterocele prolapse almost always occurs in infancy, we have treated a 17-year-old with prolapse as the initial presentation.[27] The prolapse can be significant, precluding visualization of the urethra and vagina. Bladder outlet obstruction secondary to the prolapsed tissue is a urologic emergency. Manual reduction of the prolapse may require an anesthetic and can be difficult. Once the prolapse is reduced, a Foley catheter should be left indwelling for a short time. Definitive surgical therapy should follow.

Despite the distortion, the gross appearance of the prolapsed ureterocele is usually easily distinguished from that of other interlabial masses. The tissue is eccentric, and the urethral meatus may not be visible. The prolapsed mucosa is pink in acute cases but exhibits various stages of congestion later (see Fig. 36-5D). If the diagnosis is in question, renal and bladder ultrasonography or aspiration with a fine needle is helpful.[16] Subsequent evaluation of the ureterocele includes an ultrasound study, voiding cystourethrogram (VCUG), and assessment of upper tract function.

Sarcoma Botryoides

The possibility of a genitourinary malignancy is understandably the greatest concern of the referring physician and parent when an interlabial mass is discovered. Fortunately, genitourinary malignancies in the pediatric population are uncommon, and the gross appearance of *sarcoma botryoides*, in particular, is quite distinctive. Sarcoma botryoides is a polypoid form of embryonal rhabdomyosarcoma (RMS). The tumor originates in the subepithelial layer of a hollow pelvic organ, and it protrudes into the lumen as it grows. In females, the tumors arise in the bladder or vagina or, rarely, from the uterine cervix. The polypoid tissue resembles a "bunch of grapes" and extends or prolapses into the interlabial region from the urethra or vagina (see Fig. 36-5E). RMS of the bladder usually occurs in patients younger than 5 years of age. The mean age at diagnosis for vaginal tumors is less than 4 years, and uterine tumors manifest in adolescence.[28]

Cystoscopy and vaginoscopy with biopsy are required for diagnosis, but there is no role for attempted complete endoscopic resection. Computed tomography of the chest, abdomen, and pelvis, as well as nuclear bone scanning and bone marrow aspiration, complete the tumor staging. Historically, genitourinary RMS was managed with aggressive or exenterative resection, but contemporary protocols are multimodal and attempt to minimize acute toxicity, with preservation of pelvic organs and quality of life.[28-30] Vaginal sarcoma botryoides in children is quite chemosensitive. The prognosis for a vaginal RMS is better overall than for cervical RMS, but a single polypoid cervical lesion may have the best prognosis. Polypectomy with or without curettage can be curative, but limited adjuvant chemotherapy may be advised, based on prognostic features.[31-35]

Reassessment of the tumor burden after induction chemotherapy with vincristine and actinomycin D, with or without cyclophosphamide, leads to further chemotherapy in responders and surgical excision or radiation therapy in nonresponders.[18,30,31] The most current protocols are available on the Web site of the National Cancer Institute (www.cancer.gov [accessed February 2009]).[36] The philosophical approach regarding the role of radiation and surgery differs between RMS study groups in the United States and those in Europe,[37] but the groups share a commitment to longitudinal follow-up of survivors. Organ-sparing protocols after incomplete response to chemotherapy include radiation, but late surgical intervention for treatment-related complications is common after radiation for pelvic RMS.[38]

DEVELOPMENTAL ABNORMALITIES OF THE FEMALE GENITAL TRACT

A variety of developmental abnormalities affect the internal female genital tract. These uterine and vaginal abnormalities can be divided into two categories: (1) agenesis or atresia, and (2) fusion abnormalities. The pathogenesis of these abnormalities is discussed in the following sections, as are surgical methods of vaginal reconstruction or replacement.

Normal Embryology of the Female Genital Tract

Induction of the müllerian (paramesonephric) duct as an indentation of the dorsal coelomic mesoderm is initiated by the ipsilateral mesonephric duct. The cranial portion of the müllerian duct canalizes to form the fallopian tube. The caudal portions migrate anterior and medial to the mesonephric ducts to fuse in the midline as the uterus. The fused structure (Müller tubercle) grows caudally to contact the UGS between the mesonephric ducts. Epithelial proliferation at this point of contact becomes the vaginal plate. The vaginal plate grows cranially to separate the uterus from the UGS, and ultimately it canalizes to form the vagina (Fig. 36-6).[39,40] The hymen results from epithelial proliferation at the junction between the vaginal plate and the UGS.[41]

Migration and fusion of the müllerian ducts between 6 and 12 weeks of gestation is temporally related to mesonephric duct differentiation and renal induction. This relationship explains the high frequency with which renal anomalies and genital tract anomalies coexist.[40,42]

Müllerian Agenesis

Mayer-Rokitansky-Küster-Hauser syndrome is a constellation of müllerian, renal, and skeletal abnormalities that occurs in 1 of every 4000 to 5000 46,XX females.[6,43] Deficiency of the caudal portions of the bilateral paramesonephric ducts results in failure of formation of the proximal vagina and uterus (Fig. 36-7). A well-timed embryologic omission or event may explain the constellation of findings.[44,45] Complete agenesis of the middle and upper vagina uniformly occurs, but the anatomy of the uterus and fallopian tubes is variable. A hymenal rim and vaginal dimple usually are present, because these structures are derived from the UGS. The labia and ovaries are also embryologically distinct and therefore normal. Although absence of the vagina may be noted on physical

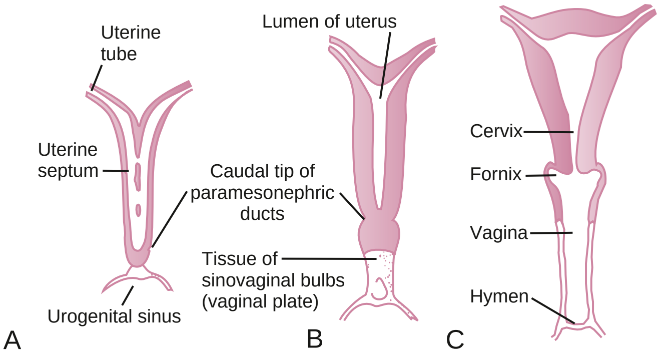

Figure 36-6 Embryology of the female genital tract. **A,** Fusion of paramesonephric ducts. **B,** Induction of vaginal plate. **C,** Canalization of the vaginal plate. (**A-C**, From Sadler TW. *Langman's Medical Embryology*. 7th ed. Baltimore: Williams & Wilkins; 1995:296.)

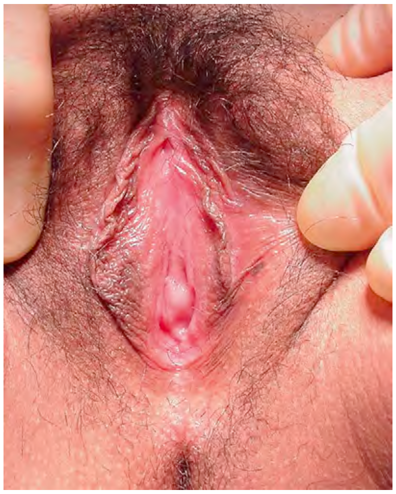

Figure 36-8 Vaginal agenesis.

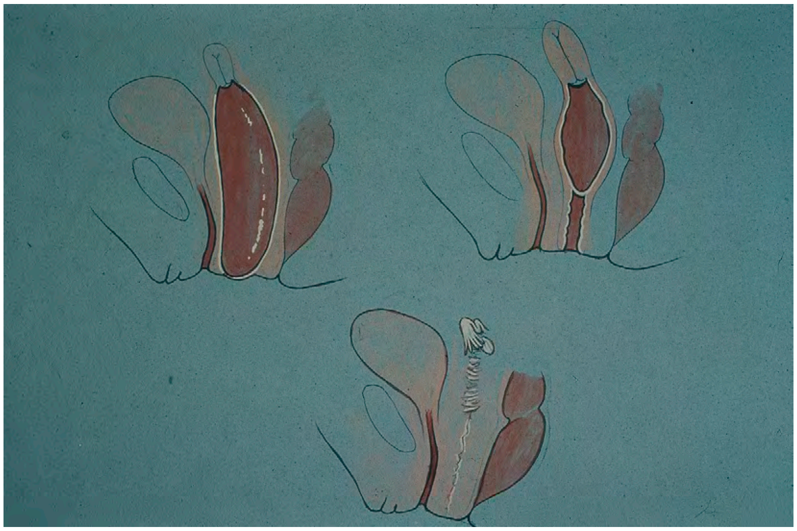

Figure 36-7 Müllerian agenesis and vertical fusion abnormalities: *Top left*, Imperforate hymen. *Top right*, Transverse septum. *Bottom*, Müllerian agenesis. (From Yerkes E, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol.* 2002;14:12-30. Copyright 2002, Medical Economics.)

examination (Fig. 36-8), primary amenorrhea is the more common presentation.[42,43,45,46] Other patients present with dyspareunia or failed intercourse.[46]

Two distinct forms of Mayer-Rokitansky-Küster-Hauser syndrome have been described.[46,47] Type A patients have symmetric residual muscular müllerian anlagen and normal fallopian tubes. Type B is the slightly more common "atypical" form, with asymmetry of the muscular buds and abnormally developed fallopian tubes. Up to 10% of patients develop cyclic abdominal pain from a small amount of functioning endometrium in a unicornuate uterus. Minor ovarian abnormalities have been reported in 15% of all cases, but only in type B patients.[46]

Associated anomalies of the upper urinary tract, most commonly renal agenesis or ectopia, have been reported in approximately one third of all cases of müllerian agenesis.[42,45,46] Skeletal abnormalities, most commonly involving vertebrae, have been reported in 10% to 20% of cases.[44,45] The renal and skeletal abnormalities seem to occur only in the type B, or atypical, cases.[44,46] Müllerian agenesis may be associated with Klippel-Feil syndrome, which involves congenital fusion of the cervical vertebrae. These anomalies are linked in the *mü*llerian duct aplasia, *r*enal aplasia, and *c*ervical *s*omite dysplasia (MURCS) association. Female genital duct anomalies, renal agenesis, and deformities of the cervical spine, ribs, and upper extremity can be explained by an embryologic malformation of the cervical somites.[44,48]

Vaginal Atresia

Failure of the UGS to form the distal portion of the vagina results in vaginal atresia. The upper vagina, uterus, fallopian tube, and ovaries are generally normal. Patients typically present with primary amenorrhea and pain or a mass related to retained menses *(hematometrocolpos)*. Treatment involves incision and dissection through the atretic segment with pull-through of the distended proximal vagina.

Abnormalities of Vertical Fusion

Normal vaginal development depends on interaction between the müllerian ducts and the UGS. Incomplete canalization at the urogenital membrane or at various levels of the vaginal plate results in an imperforate hymen or a transverse vaginal septum, respectively (see Fig. 36-7). If an imperforate hymen is not detected on examination or as a result of mucocolpos, the abnormality is likely to go undetected until menarche.

Although a very low transverse vaginal septum may rarely manifest as a bulging perineal mass in the neonate, most transverse septa are discovered in the evaluation of primary amenorrhea. A history of subtle cyclic abdominal pain may be elicited, or the patient may give history of frank *cryptomenorrhea* (menstrual symptoms without the efflux of menstrual blood). Hematometrocolpos results from retention of menstrual products. The obstruction needs to be addressed to relieve symptoms and to preserve fertility.

Imperforate hymen is treated with hymenotomy. As with distal vaginal atresia, a low transverse vaginal septum can be divided transvaginally with pull-through of the distended proximal vagina. High or thick septa usually require a complex vaginal replacement to provide normal uterine drainage.[42,49] After relief of the obstruction, patients with vertical fusion abnormalities are capable of achieving and maintaining pregnancy. A history of imperforate hymen does not seem to predispose to primary infertility or fetal loss, but patients with a prior transverse vaginal septum have a higher rate of spontaneous abortions. Chronic backflow of retained menstrual fluids can result in significant endometriosis with associated infertility.[49] A distended proximal segment facilitates reconstruction, but temporary menstrual suppression may be prudent if the young woman is not physically or emotionally ready to undergo complex vaginal reconstruction.

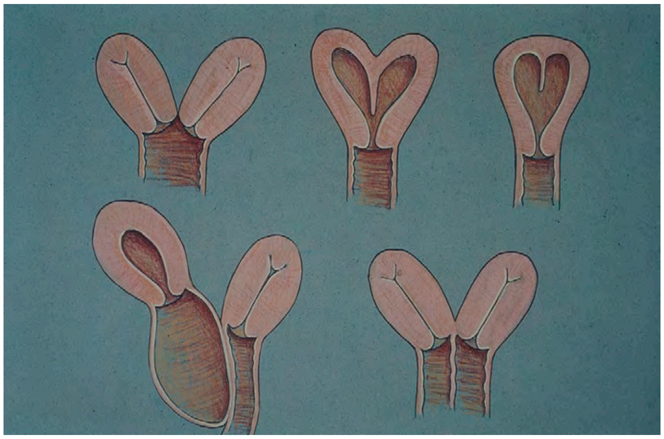

Figure 36-9 Abnormalities of lateral fusion. *Top left,* Septate uterus. *Top middle,* Bicornuate uterus. *Top right,* Uterus didelphys. *Bottom left,* Uterus didelphys with vaginal septum. *Bottom right,* Uterus didelphys with obstructed hemivagina. (From Yerkes E, Rink RC. What urologists should know about pediatric gynecologic abnormalities. *Contemp Urol.* 2002;14:12-30. Copyright 2002, Medical Economics.)

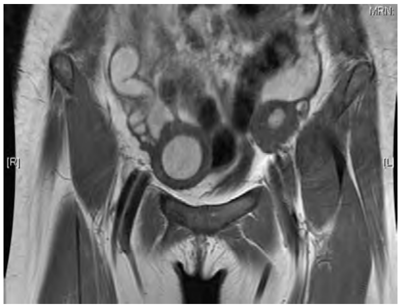

Figure 36-10 Coronal magnetic resonance image of obstructed uterine horns in an adolescent who underwent rectal pull-through as an infant. No vaginal orifice is present on examination of perineum.

Abnormalities of Lateral Fusion

Failure of the uterine anlagen to fuse in the midline results in a spectrum of genital tract abnormalities, and unilateral müllerian hypoplasia may be present (Fig. 36-9). The uterus may be unicornuate, septate, or bifid. There may be complete duplication of the uterus and cervix *(uterus didelphys)* with a longitudinal vaginal septum. All patients with unilateral maldevelopment of the müllerian duct have either ipsilateral renal agenesis or ectopia; the majority have agenesis.[6]

Lateral fusion anomalies are usually asymptomatic until child-bearing years, although an obstructed uterine horn (Fig. 36-10) or an obstructed hemivagina can result in cyclic abdominal pain with onset of menses. An obstructed hemivagina is adequately addressed by wide transvaginal marsupialization of the vaginal septum.[40]

VAGINAL REPLACEMENT

A wide variety of techniques for vaginal reconstruction or replacement in patients with vaginal agenesis have been employed over the last 2 centuries. Similar principles are applied to reconstruction of high, thick transverse septa and in cases of complete androgen insensitivity syndrome (CAIS). Multiple modifications of several classic procedures have led to a number of suitable vaginal substitutes. Many reasonable options exist, and the surgeon should work with the patient to determine the most appropriate approach (Tables 36-1 and 36-2).[50]

Timing of reconstruction remains controversial and depends not only on the nature of the underlying abnormality (e.g., obstruction of functioning endometrium versus agenesis) but also on the type of reconstruction planned. Mature patients may be more diligent about the routine dilations that often are required after replacement vaginoplasty. Although pelvic ultrasonography or computed tomography may have been performed during evaluation of the müllerian or vaginal abnormality, magnetic resonance imaging (MRI) and transperineal ultrasonography provide valuable preoperative information. MRI clearly demonstrates the existing müllerian structures and hydrometrocolpos, and sagittal views reveal the level and thickness of a transverse vaginal septum or the length of an atretic vagina.[51] Transperineal ultrasonography provides similar important information about the extent of the vaginal defect.[52] Preoperative knowledge of the level and extent of the vaginal defect guides surgical therapy and helps prevent inadvertent injury to surrounding organs during the course of dissection.

Progressive Dilation

In 1938, Frank[53] proposed the creation of a neovagina by applying progressive pressure to the perineum or vaginal dimple in patients with vaginal agenesis. Ingram[54] modified the technique with the use of dilators mounted on a bicycle seat. The dilation occurs over several months. This technique is not adequate for all patients, but a neovagina can be successfully created nonoperatively in some highly motivated patients.

The Vecchietti operation, which applies Frank's principle via an abdominal traction device, was introduced in 1965. The dilation procedure is completed over 7 to 9 days with this invasive

Table 36-1 **Considerations for Vaginal Replacement**

Outcomes (see Table 36-2)
Surgeon Expertise
Patient Preference
Motivation for nonoperative techniques
Age/maturity/readiness for physical relationship
Willingness to accept long-term dilation
Cosmetic concerns (donor site, laparotomy scar)
Patient Factors
Presence of functional uterine segment ± proximal vagina
Size and pliability of vaginal dimple
Prior abdominal and pelvic procedures
Need for concomitant reconstructive procedures
Prior pelvic irradiation
Personal or family history of inflammatory bowel disease

Table 36-2 **Factors in the Quest for the Ideal Vaginal Replacement**

Outcomes
Function: natural position, size, sensation, secretions
Need for dilation to achieve or maintain functional size
Risk of prolapse
Risk of malignancy or other secondary change
Patient
Level of satisfaction with function and cosmesis
Morbidity/Disruption of normal daily activities
Time until first intercourse

approach.[41] Laparoscopic modifications of the Vecchietti operation have also been described.[55,56] Long-term dilation is required to maintain adequate caliber. Progressive dilation techniques are not widely used by urologists at this time.

Vulvovaginoplasty

In 1964, Williams[57] described a superficial vulvovaginoplasty for the creation of a neovagina in women with vaginal agenesis. Although a satisfactory channel can be created, the angle of the vagina is quite abnormal, and voided urine may pool in the vagina.[41] Others have tubularized hairless vulvar flaps and rotated the neovagina into the bluntly dissected rectovesical space. The cavity then requires progressive enlargement with Lucite dilators.[58] Johnson and coworkers[59] described the use of labia minora tissue expanders in preparation for vaginoplasty. They found the outcome satisfactory, without the need for chronic dilation, but the risk of infection with expansion is significant.

Rectovesical Space Dissection and Vaginal Molds

After bluntly dissecting the rectovesical space to a caliber adequate for a functional vagina, innovative surgeons have used various tissues over vaginal forms to create a neovagina. The vaginal molds of historical interest include gauze packing, balsa wood, and Pyre glass plugs.[60] In 1960, Sheares[60] described an anatomic technique for dissecting the rectovesical space that allowed blunt canalization of the vestigial müllerian structures with subsequent excision of the fibrous midline septum. His planes of dissection avoided significant bleeding and reduced the risk of bladder or rectal injury.

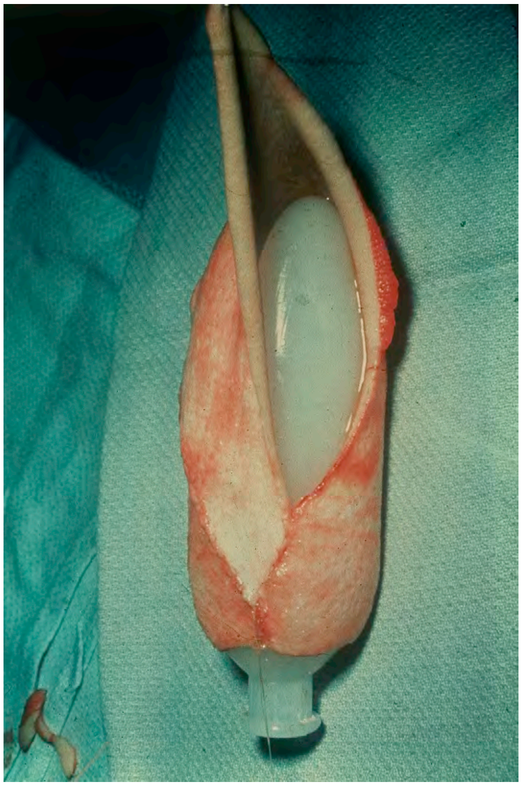

Figure 36-11 Abbe-McIndoe procedure: split-thickness skin graft sewn over a vaginal mold.

Initial procedures allowed gradual epithelialization around the vaginal mold. Split-thickness skin grafts were sewn over a vaginal mold in the classic Abbe-McIndoe procedure, which was overall one of the most common techniques employed in the history of vaginal replacement (Fig. 36-11). It is used much less commonly today. Although results are generally satisfactory with this technique, dilations are required, and contraction of the graft can be a significant problem.[41,61] Hendren and Donahoe[62] found thick grafts to be more successful. Peritoneum,[63,64] human amnion,[65] bladder mucosa,[64] buccal mucosa,[66] and Interceed absorbable barrier[67] have all been used over vaginal molds.

Bowel Interposition

Vaginal replacement with intestine is the method of choice for most urologists. Pedicled bowel interposition grafts have several distinct advantages over vaginoplasties that utilize skin grafts or flaps. The need for laparotomy and the risk of pelvic contamination were previous limitations, but greater facility with laparoscopic dissection and use of endostapling devices minimize these concerns in selected patients. Contractures of the bowel segment are uncommon, and dilation usually is not required. Intestinal mucus provides lubrication of the neovagina and is easily managed with douching in most patients. Satisfaction with sexual function is reported by more than 75% of women after bowel vaginoplasty.[68]

Initially, Baldwin[69] proposed a U-shaped ileal or sigmoid vagina, but subsequent efforts have used linear segments. We have obtained excellent results with sigmoid vaginoplasty, as have others.[64,70-72] The sigmoid is ideally suited for mobilization into the rectovesical space. In a patient with prior pelvic surgery or irradiation, the cecum is a more appropriate choice. Ileum is less desirable because of its smaller circumference and more restrictive mesentery. If the mesentery is under tension as the ileal segment is brought toward the perineum, ischemia and stenosis may result.[71] Periumbilical cramping during intercourse has also been reported with ileal grafts.[64,72]

Before bowel vaginoplasty, the patient should have mechanical and antibiotic bowel preparation. Positioning the patient in the low lithotomy position allows access to the abdomen and the perineum, whether the procedure will be completed by laparotomy or laparoscopic assistance. Dissection from the perineum prepares the rectovesical space to accept the bowel segment. Regardless of the abdominal approach, a 8- to 10-cm segment of sigmoid colon is isolated on the left colic or superior hemorrhoidal artery (Fig. 36-12A). Bowel continuity is restored with stapled or hand-sewn colocolostomy. The sigmoid segment can be advanced to the perineum in an isoperistaltic fashion, or it may be rotated 180 degrees on its mesentery to obtain a tension-free anastomosis at the perineum (see Fig. 36-12B). This anastomosis is performed with interrupted absorbable sutures. The proximal portion of the vagina is oversewn in two layers or is anastomosed to the uterus, if present. Two-point fixation between the proximal neovagina and the retroperitoneum prevents migration of the bowel segment.[71]

Avoidance of overlapping suture lines is important in the prevention of colovaginal fistula. Hendren and Atala[70] described intentionally discarding the most proximal segment of the isolated sigmoid while allowing the vascular pedicle to remain with the sigmoid vagina. This maneuver often lengthens the pedicle but also prevents the proximal vaginal closure or anastomosis from resting over the colocolostomy.

If a native distal vaginal segment is present, it can be pushed toward the pelvic cul de sac with a Hegar dilator and opened widely for anastomosis to the bowel.[71] Alternatively, if adequate tissue is present, a perineal or labial flap may be used for the same purpose. These maneuvers are advantageous, because they allow a wider anastomosis and prevent a cicatrix at the introitus. Hensle and Dean[71] recommended leaving a syringe, wrapped in antibiotic-impregnated gauze, in the neovagina for 5 days. If examination at 3 weeks or 3 months reveals any evidence of introital stenosis, manual dilation under anesthesia can be performed. This usually eliminates the need for further dilation. Late introital stenosis may require Z-plasty or other local modification.[70]

Minor eversion of the bowel mucosa is common,[70] but redundant mucosa can be trimmed easily as an outpatient procedure. Significant prolapse or intussusception of the graft is uncommon and can be avoided by two-point fixation of the proximal vagina to the retroperitoneum.[71]

Myocutaneous and Fasciocutaneous Flaps

As with other forms of vaginal substitution, dissection of the rectovesical space is required before rotation of myocutaneous flaps. This technique is most commonly used for reconstruction after pelvic exenteration. Gracilis flaps afford good results,[73] but the thigh scars are disfiguring. Pudendal thigh flap incisions are more camouflaged within the groin.[74,75] Creation of a sensate neovagina is a theoretical advantage with myocutaneous flaps, and these flaps do not require chronic dilation.

Long-Term Issues After Vaginal Replacement

Many years after vaginal reconstruction, some patients continue to be troubled with stenosis or contracture if regular dilations or intercourse is not practiced. Internal contracture usually is not an issue after sigmoid vaginoplasty. Other long-term concerns for young women undergoing vaginal replacement include parturition, malignancy, and inflammatory diseases. For those women who have functioning endometrium and fertility potential, the suitability of the neovagina for delivery of a term infant comes into question. Although an intestinal neovagina may be quite distensible, delivery by cesarean section is prudent after vaginal replacement procedures.

Carcinoma within the neovagina manifests with clear or bloody vaginal discharge or postcoital bleeding. It is

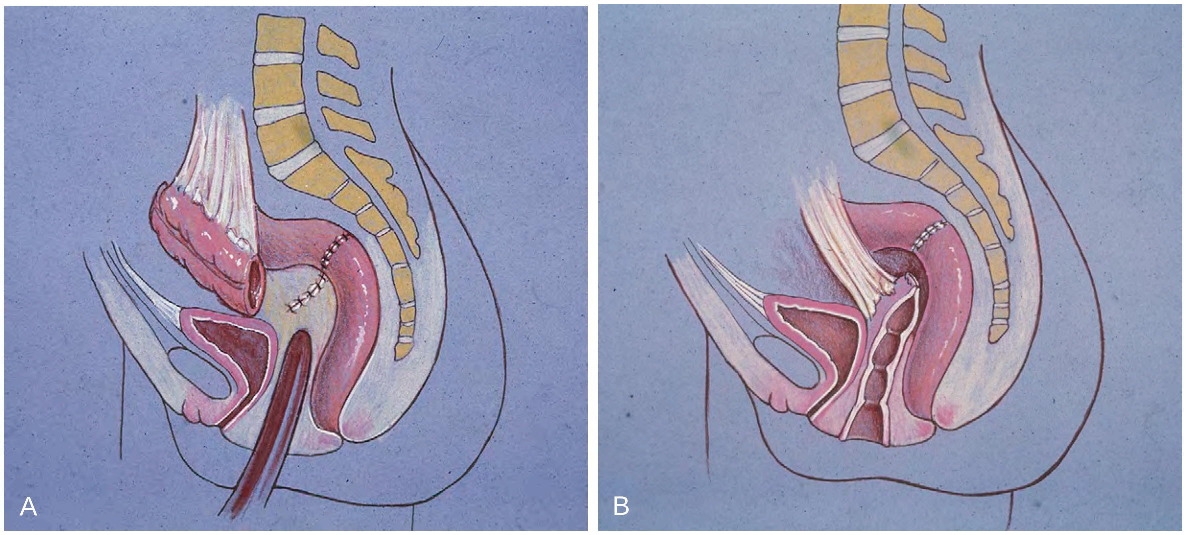

Figure 36-12 Colon vaginoplasty. **A,** Dissection of rectovesical space for excluded bowel segment. **B,** Completed sigmoid vaginoplasty.

distinct from primary vaginal carcinoma in that it occurs in much younger women, and the histologic type reflects the tissue from which the neovagina was created, with squamous cell carcinoma occurring in skin grafts or flaps and adenocarcinoma occurring after intestinal substitution. Potential contributing factors include granulation tissue, foreign flora, irritation from dilators or intercourse, and viral exposures. The rate of carcinoma in the neovagina does not appear to be greater than the incidence of primary vaginal cancer, but knowledge of the potential for malignant changes highlights the importance of routine pelvic examinations and long-term follow-up after any form of vaginal replacement. Biopsy is required for diagnosis, and definitive treatment is surgical.[76]

Chronic inflammatory conditions of the colon may also affect the colonic neovagina. Ulcerative colitis has been seen in colonic neovaginas, with vaginal bleeding presenting in concert with colicky pain and rectal bleeding.[77] Diversion colitis occurs in colonic segments isolated from the fecal stream, due to lack of surface contact with short-chain fatty acids and their trophic and maintenance effects on the epithelium. Vaginal discharge or bleeding occurs secondary to edema and fragility of the epithelium, and remission may be achieved by short-chain fatty acid irrigations.[78] Either of these inflammatory conditions could increase the risk of adenocarcinoma.[76]

UROGENITAL SINUS ANOMALIES AND DISORDERS OF SEX DEVELOPMENT

UGS anomalies are among the more complex genitourinary anomalies and require thorough preparation and meticulous surgical technique. Incomplete embryologic separation of the UGS into the urethra and female genital tract occurs along a spectrum, with the urethra and vagina sharing a distal common channel to the perineum. The confluence may be near the perineum or as high as the level of the bladder neck. UGS anomalies occur most commonly in association with congenital adrenal hyperplasia (CAH), but pure UGS anomalies without clitoromegaly or endocrinologic abnormalities also occur. Cloacal malformations take the UGS anomaly one large step further by confluence with the hindgut. Female exstrophy-epispadias (see Chapter 30) is another form of UGS anomaly with anterior displacement of the urogenital complex. This section focuses on evaluation and management of UGS associated with disorders of sex development and the pure UGS. Cloacal anomalies are addressed in the final section.

Initial Evaluation

Because most patients with UGS anomalies present as neonates with genital ambiguity, the initial management centers on identifying potentially life-threatening problems and gathering sufficient data to allow timely assignment of gender. Ideally, a multidisciplinary team consisting of at least a neonatologist, an endocrinologist, a urologist or pediatric surgeon, and a consistent child psychologist or social worker gathers these data and works with the parents. Genetic counseling is appropriate. This is an extremely stressful time for most parents, and it is the beginning of a critical long-term relationship between the family and the multidisciplinary team. The infant is the passive center of the team at this point but ultimately has the most important voice. The family will have many questions that the surgeon may not be fully equipped to answer. The Intersex Society of North America has published a resource, by and for families and individuals with disorders of sex development, addressing many of these concerns.[79] It is available online at www.dsdguidelines.org (accessed February 2009).

CAH secondary to 21-hydroxylase deficiency is the most common diagnosis. The details of the enzymatic defects and long-term medical management of the various forms of CAH are discussed in Chapter 35.

History and Physical Examination

A careful history and physical examination often lead toward the correct diagnosis. Pertinent elements of the history include maternal ingestion of androgenic substances, evidence of maternal virilizing tumor, and prior fetal demise. A family history of neonatal death, genital ambiguity, or gender dissatisfaction is also relevant.

Begin by assessing the overall well-being of the child, although clinical issues secondary to salt-wasting forms of CAH are not typically seen within the first days of life. The back and abdomen are examined for neurocutaneous abnormalities or a suprapubic mass suggesting hydrocolpos or a distended bladder. The size and consistency of the phallic tissue and the relative position of the labioscrotal folds are documented. The location, size, and consistency of the gonads must be noted. The number of perineal orifices and their locations should be noted. The anus may be anteriorly displaced, so its location and patency should be documented.

Radiographic and Endoscopic Evaluation

Radiographic and endoscopic evaluation are important in planning the surgical approach. Both are performed to delineate the anatomy and should identify the length of the common sinus, the location of the confluence of the vagina, the distance from the vaginal confluence to the bladder neck, the number of vaginas, the presence of a cervix, and the contour of the bladder. Genitography is performed by occluding the perineal orifice with a balloon catheter. Contrast material is injected in a retrograde fashion, with lateral and oblique views obtained. The catheter should then be passed into the bladder for standard VCUG. Genitography has limited usefulness in CAH. Endoscopy is even more helpful in understanding the anatomy and is usually postponed until the time of reconstruction unless genitography findings are confusing. Hendren and associates[80,81] noted that they often visualized an external male-type sphincter in extremely virilized females (Fig. 36-13). If this is present, its location in relation to the vaginal confluence should be documented, but in our experience a well-defined sphincter is extremely rare.[82]

Ultrasonography can be helpful in identifying the uterus, vagina, and gonads. A distended bladder or vagina or concomitant renal anomaly may be noted. The adrenal glands should be examined, because a serpiginous appearance is indicative of CAH.[83] In the rare situation in which the anatomy remains confusing, MRI of the pelvis may be helpful. We have seen two patients with duplicated vaginas side by side and duplicated bladders one on top of the other, demonstrating the complexity of the anatomy at times.[84]

Rarely, the correct diagnosis requires gonadal biopsy. This can be done laparoscopically, but a deep, full-length gonadal biopsy should be obtained, because the ovarian tissue may be completely surrounded by testicular tissue.[85] Griffin and Wilson[86] observed that genital skin biopsy may be helpful in the diagnosis of androgen insensitivity or 5-α reductase deficiency.

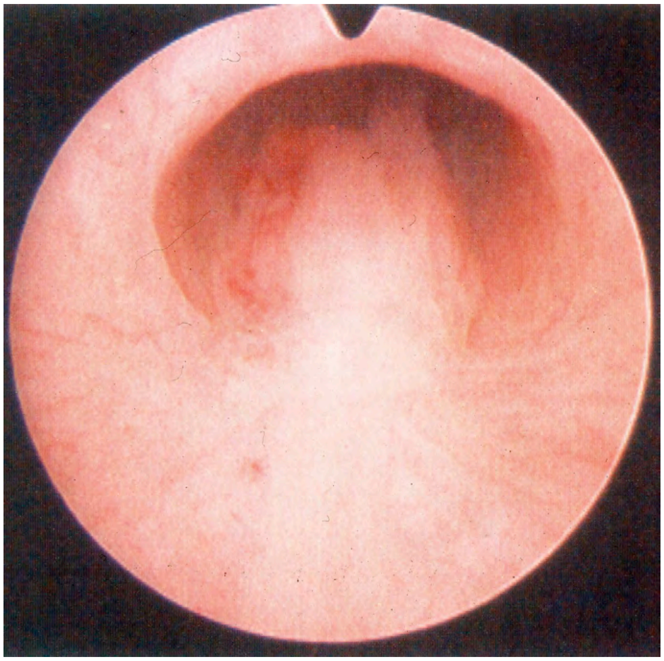

Figure 36-13 Urogenital sinus with a male-type external sphincter. Vaginal confluence is within the fleshy tissue that resembles the verumontanum.

Surgical Reconstruction of Urogenital Sinus Anomalies and Disorders of Sex Development

Philosophy

Most patients found to have UGS abnormalities have underlying disorders of sexual development (intersex) with genital ambiguity. In these children, clitoral enlargement and other associated forms of genital masculinization, such as labial fusion, are a source of great concern for the parents. It is a common belief that early surgery to "normalize" the genitalia helps promote attachment between parent and infant, but there is little evidence to support either this bias or the opposite position. Surgical techniques to achieve this objective offer nice cosmesis and increasing evidence for preserved sensation with contemporary nerve-sparing clitoroplasty.[87,88] In an effort to minimize irreversible surgical acts, Pippi Salle and associates reported a nerve-sparing and corpora-sparing clitoroplasty.[89]

Long-term data regarding sexual function and satisfaction with genital appearance in women with CAH, with or without clitoral surgery during childhood, are limited due to the inclusion of mixed and often outdated surgical techniques in published reports. The surgeon and family must realize that feminizing genital surgery is very controversial at this time. The timing of reconstruction and whether reconstruction should be done at all are currently in question by both intersex advocacy groups and those in the medical field. Some have even called for a moratorium on sex assignment cosmetic surgery in all patients until they are at an age at which they can make their own decisions.[90] An international panel of experts recently published a consensus statement on the management of children with intersex disorders, including the recommendation for less pejorative terminology (i.e., "disorders of sex development"). Chromosomal sex, gonads, hormonal milieu, phenotype, and fertility potential are all considered in gender assignment. The parents should understand that our best collective effort to assign the appropriate gender may not yield the best answer.[91] We believe that parents should be presented with all options and scenarios for the future. The role of the surgeon and multidisciplinary team is to help the family make informed decisions without dictating the need for genital surgery.

There is strong evidence that female patients with CAH will identify and live as women despite androgen exposure in utero,[91] so consideration of feminizing surgery is less controversial in this group. Feminizing genitoplasty for genital ambiguity associated with a UGS anomaly involves three steps: (1) clitoroplasty, (2) vaginoplasty, and (3) labioplasty. The trend since the early 1990s has been toward earlier reconstruction of all three components, although this approach has again been called into question. There has been no agreement regarding timing, necessity, and likelihood of harm from genital surgery in infancy and childhood,[92] but the proposed guidelines for management of disorders of sexual development are a consensus from international experts in all related disciplines.[79,91] Early reports of genital reconstruction did not note an optimal time for clitoroplasty, but by the late 1960s and early 1970s, clitoroplasty was thought to be appropriate by 1 year of age.[93,94] In 1995, DeJong and Boemers[95] reported reconstruction as early as 1 to 3 weeks of age.

The timing for vaginoplasty is also controversial, with two opposing but rational viewpoints. One group believes that clitoroplasty, vaginoplasty, and labioplasty should be done in a single procedure early in life. This allows all native genital tissue to be available for reconstruction, with less scarring.[81,95-99] We have previously stated a preference for this approach.[100] Maternal estrogen stimulation thickens the vaginal and paravaginal tissues, making vaginal mobilization easier in the neonatal period.[95,96,101,102] The other group believes that vaginal stenosis is common after early surgery for a high vaginal confluence and that such patients often require repeated long-term vaginal dilations and later secondary vaginoplasty. They recommend delaying vaginoplasty until after puberty.[103-106]

Gradual modifications in technique and the inherent lag time between the surgical procedure and any promise of functional outcomes data continue to limit our ability to reach a consensus. In this chapter, we describe a single-stage feminizing genitoplasty, but the vaginoplasty techniques could also be used in a two-stage approach. The techniques are applicable to both neonates and adolescents.

Techniques

The surgical approach to clitoral hypertrophy has evolved dramatically since the recognition that cosmesis is only one element of the desired optimal surgical outcome. Moving beyond the initial reports of clitoral resection,[80,93,107] various techniques for clitoral recession were described.[108-111] Several contemporary variations share the common objectives of preserving the neurovascular integrity of the glans clitoris, preventing painful erections and providing feminine cosmesis. These new procedures have their basis in Schmid's efforts to excise corporal tissue while preserving the neurovascular bundle to the intact glans.[112] Most surgeons now use some modification of Kogan's subtunical excision of the erectile tissue.[113] Baskin and associates[114] demonstrated that circumferential branches from the dorsal neurovascular bundles wrap toward the ventrum, making a ventral approach to the corpora less concerning (Fig. 36-14). Corporal tissue proximal to the bifurcation is left intact. Engorgement of this retained but unrestrained corporal tissue may enhance sexual function, but data are lacking. Opinions vary regarding reduction of the glans clitoris.[87,89,115,116] To maximize the likelihood of preserved sensation and viability, we believe that the glans should be well concealed but left intact. Ventral modification, if any, would seem prudent. The prepuce should be preserved as the clitoral hood, because this

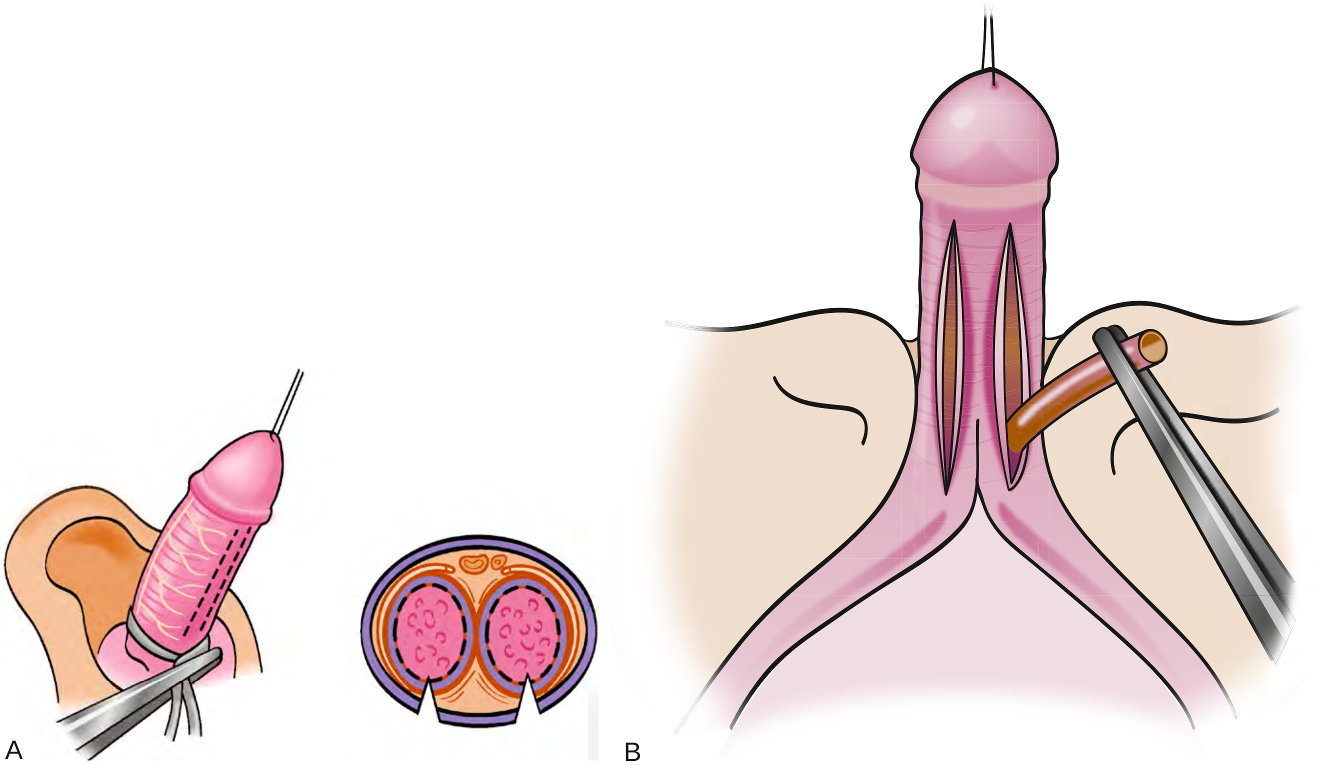

Figure 36-14 Technique for clitoroplasty. **A,** Note lateral extension of neurovascular bundle relative to planned incision. **B,** Excision of erectile tissue distal to bifurcation.

Table 36-3 Types of Vaginal Reconstruction

Cut-back vaginoplasty
Flap vaginoplasty
Pull-through vaginoplasty
Total and partial urogenital mobilization (TUM and PUM)
Vaginal replacement

is highly sensitive tissue as well.[117] If the dorsal circumcising incision is made more proximally, more of the sensitive inner prepuce is preserved for a natural hood.

The type of vaginoplasty required depends on the anatomic location of the vaginal entrance into the common UGS. Five distinct types are listed in Table 36-3. *Cut-back vaginoplasty* is used in cases of isolated labial fusion. It has no place in the management of a common UGS.

Flap vaginoplasty is based on the description by Fortunoff and associates[118] of an inverted-U perineal skin flap that could be advanced into the opened UGS and vagina. It should be used only in the setting of a low confluence. The procedure opens or widens the UGS but does nothing to address the confluence (Fig. 36-15).[82] Although some have extended its use to a higher vaginal confluence, the result is a hypospadiac urethra with vaginal voiding, urinary infections, and incontinence.[81,101]

Pull-through vaginoplasty was described by Hendren and Crawford[80] in 1969, after they observed that the vagina in some very masculinized patients entered near the bladder neck and superior to a male-type sphincteric mechanism (Fig. 36-16). Although this procedure has been modified extensively since its original description, the concept of separating the vagina completely from the UGS, reconstructing the sinus as the urethra, and bringing the vagina to the perineum remains the basis of vaginoplasty for the high- and even some midlevel vaginal confluences. Extending the mobilized vagina to the perineum can at times be difficult, requiring skin flaps or even bowel segments to construct the distal vagina.

Total urogenital mobilization (TUM) was introduced by Alberto Peña in 1997.[119] This en bloc mobilization of the UGS was originally described for children with cloacal anomalies but has now been applied to UGS anomalies.[100,120] After circumferential mobilization, the sinus can be brought toward the perineum (Fig. 36-17A). This allows the midlevel vaginal confluence to easily reach the perineum, avoiding the need for vaginal separation as in a pull-through vaginoplasty. Even if a pull-through procedure is still required to address a very high vaginal confluence, visualization of the confluence is easier, and separation is therefore less demanding. Peña reported not only a superior cosmetic result with decreased risk of fistula and vaginal stenosis but also a 70% decrease in operative time.[119] The excess mobilized sinus was discarded in the reports of both Peña[119] and Ludwikowski and colleagues.[120] We recommend splitting the excess mobilized sinus tissue longitudinally for use as a mucosa-lined vestibule or to complete the vaginoplasty (Fig. 36-18).[121]

Partial urogenital mobilization (PUM) was described by Rink and colleagues[122] for shorter common channels. PUM offers similar benefits in terms of limiting the need for pull-through vaginoplasty, but dissection stops at the pubourethral ligament to avoid damage to the delicate innervation of the bladder outlet and clitoris and preserve the support of the pubourethral ligament (see Fig. 36-17B). Early results in terms of cosmesis, continence, and vaginal caliber are favorable.[122,123]

Complete vaginal replacement is used in those patients with an absent or rudimentary vagina. The merits of various replacement techniques were previously discussed.

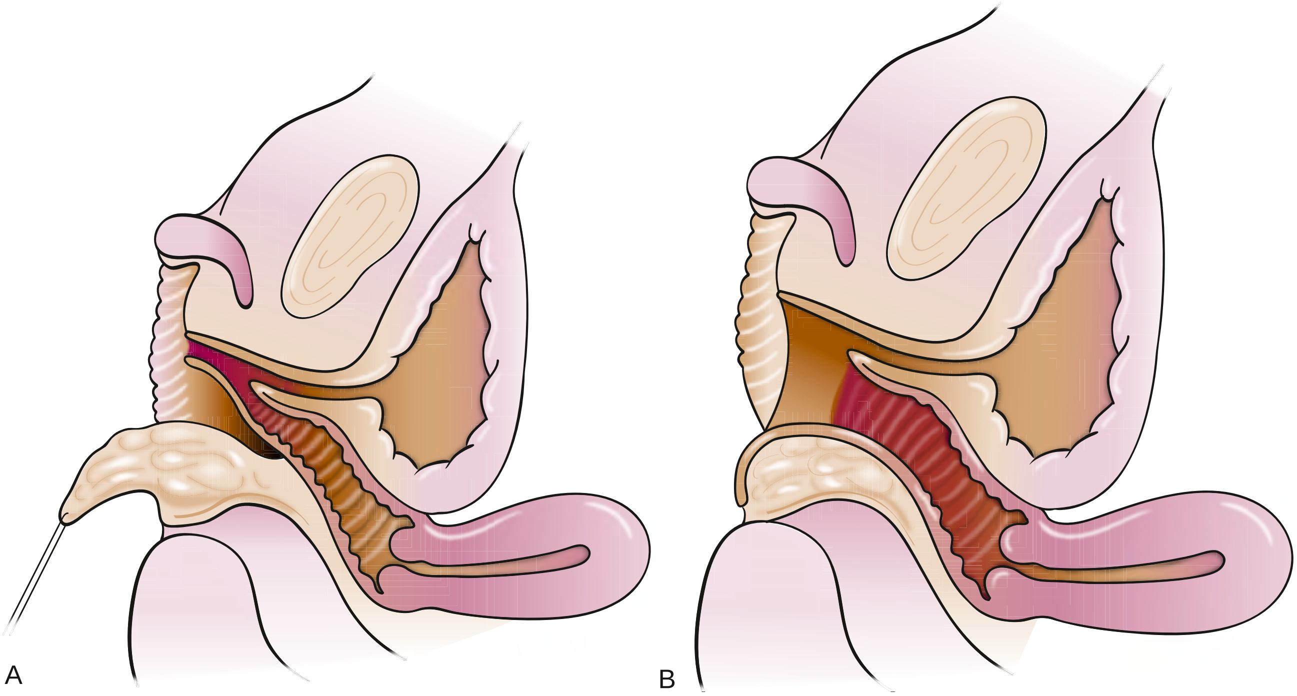

Figure 36-15 Flap vaginoplasty. **A,** Flap is mobilized prior to incision of the sinus. **B,** Note that confluence is not changed, but the sinus is opened up by insertion of the flap.

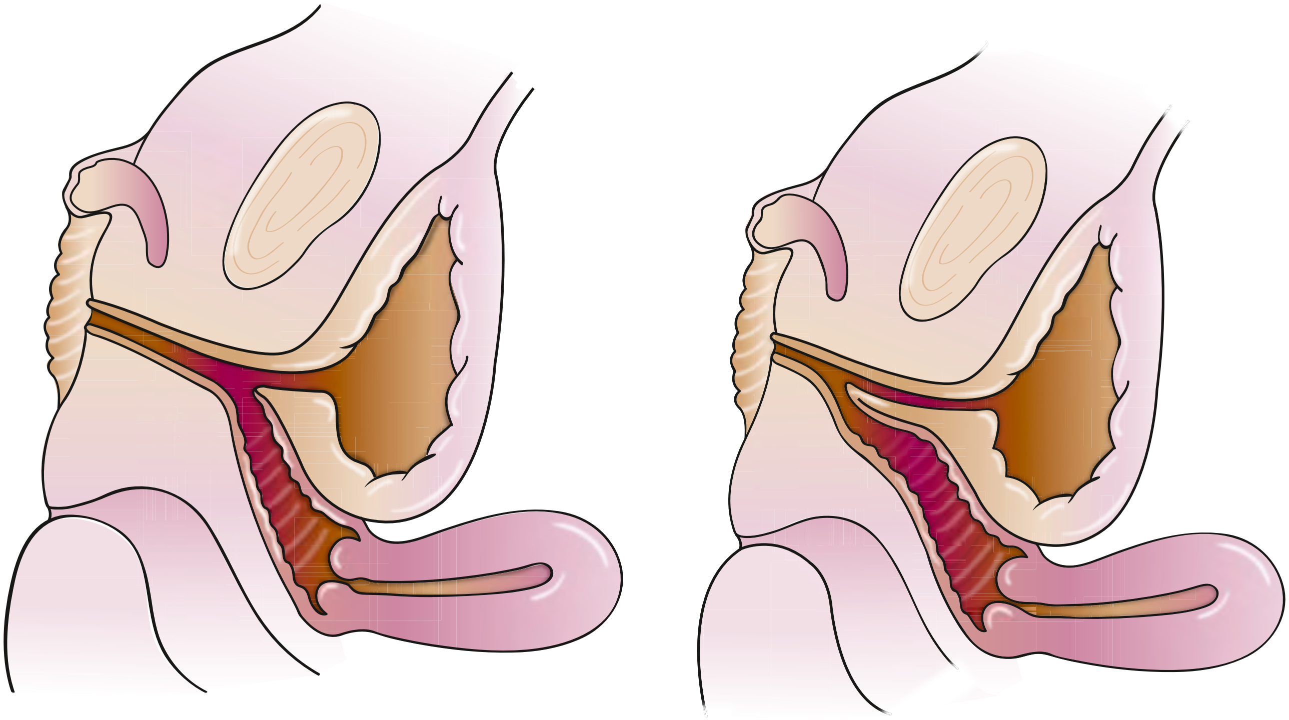

Figure 36-16 Sagittal view of low *(right)* and high *(left)* vaginal confluence.

Preoperative Preparation

All children undergoing vaginoplasty require at least an enema, and the high confluence patients receive total bowel preparation using polyethylene glycol (GoLYTELY; Braintree Laboratory, Braintree, MA). If the child has CAH, preoperative stress steroids and a perioperative steroid taper should be directed by the child's endocrinologist. After induction of general anesthesia, the child is placed in the dorsal lithotomy position for endoscopy. The level of the vaginal confluence is

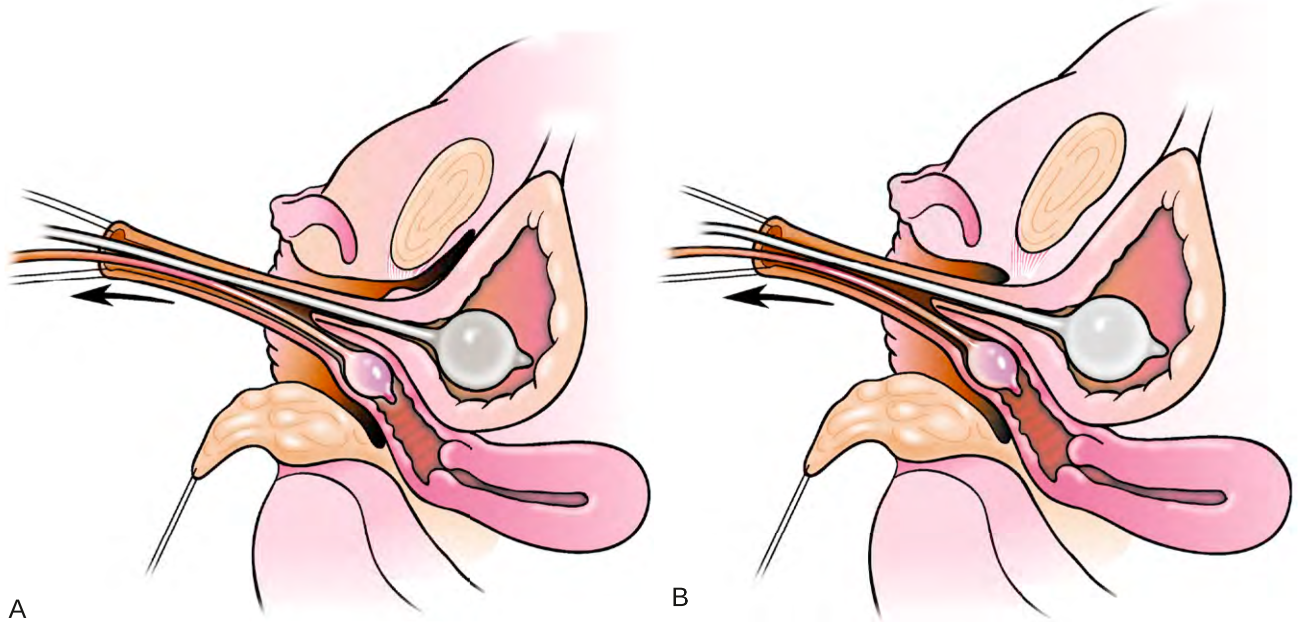

Figure 36-17 Sagittal illustration of total urogenital mobilization or TUM **(A)** versus partial urogenital mobilization or PUM **(B)**. Note that dissection stops at the pubourethral ligament in PUM.

noted, and a Fogarty catheter is passed into the vagina. The balloon is inflated, and the catheter is clamped. Endoscopy is repeated to verify correct positioning of the Fogarty catheter. A Foley catheter is then placed into the bladder. Many surgeons prefer to perform the vaginoplasty with the child in the lithotomy position, but we prefer to prepare the entire lower body from nipples to toes, front and back. This allows better vision for the assistants and offers the opportunity to place the child in either the supine or the prone position, allowing access to both the perineum and the abdomen. The legs are wrapped, and the child is passed though the aperture in the drapes (Fig. 36-19). A moist radiopaque sponge is placed in the rectum and should be retrieved at the end of the case.

Operative Details

The following sections detail the approaches to both high and low vaginal confluence, including flap vaginoplasty, pull-through vaginoplasty, and TUM or PUM. Our approach in virtually all cases now is urogenital mobilization.

Low Vaginal Confluence (Clitoroplasty, Flap Vaginoplasty, Labioplasty)

With the child supine, a traction suture is placed in the glans clitoris, and a skin scribe outlines proposed incisions. A circumcising incision is marked circumferentially, leaving a generous dorsal "collar" to form the inner aspect of the clitoral hood. Parallel lines are drawn ventrally, along the spongy urethral plate, and extending around the UGS. An inverted U- or omega-shaped perineal flap is outlined with the apex near the meatus. A Y-incision is outlined at the base of labia majora. The lines may be infiltrated with 0.5% lidocaine with 1:200,000 epinephrine for hemostasis.

The circumcising incision includes complete transection of the urethral plate. The urethral plate is dissected off the corpora, preserving the spongiosum. The entire clitoris is exposed to the bifurcation of the corporal bodies, with care taken to protect the neurovascular bundles by dissecting above Buck fascia and to avoid the deep nerves at the bifurcation. After a tourniquet is placed at the base of the clitoris, incisions are made ventromedially into the corpora, from the bifurcation to the glans (see Fig. 36-14A). The erectile tissue is excised, with care taken not to injure Buck fascia, the tunics, or the neurovascular bundle (see Fig. 36-14B). The proximal ends of the erectile tissue are oversewn. If the glans requires tailoring, this should be done ventrally and medially to preserve sensation. The glans is then sewn to the bifurcation of the corporal bodies. In our experience, if the glans is sewn to the pubis, it is often too high and too prominent. The prepuce is unfurled and divided in the midline to create labia minora. Stopping short at the base allows the skin to form a more normal clitoral hood. The mobilized urethral plate is trimmed and secured to the ventral collar of the clitoris to restore a mucosa-lined vestibule.

The flap vaginoplasty is started by incising the perineal flap and mobilizing it with its underlying fatty tissue. The UGS is exposed and is opened along the ventral aspect in the midline up into the vagina. To minimize stenosis, the incision must extend beyond the narrowed distal vagina into normal-caliber vagina. Once this is accomplished, individual Vicryl sutures are placed from the flap to the vagina.

The divided preputial skin is advanced alongside the urethral plate and introitus to create labia minora. The labia majora are now mobilized and advanced inferiorly as a YV-plasty (Fig. 36-20). The tips of particularly redundant or rugated labial flaps may be tailored to reduce bulk. A Penrose drain is left in the vagina until the patient is out of bed, and the Foley catheter is left indwelling.

High Vaginal Confluence

As noted previously, vaginal pull-through has been the procedure of choice for the high confluence, but it is now simplified by urogenital mobilization. This section addresses the traditional approach to the high confluence.

Great care must be taken, not only in this difficult dissection but also to prevent the vaginal opening from appearing isolated on the perineum.[115] Vision can be limited during the critical aspect of the procedure—separation of the anterior vaginal wall from the urinary tract. One must be meticulous in this area to avoid injury to the urethra or sphincteric mechanism. Several authors have described techniques to improve exposure. Passerini-Glazel[115] mobilized the vagina transtrigonally. Others have reported a transanorectal approach.[124-126] Rink and colleagues[100,101] proposed a posterior prone approach, which provides excellent exposure without division of the rectum or need for colostomy. A posterior prone approach is described here.

Preparation, endoscopy, and catheter placement are the same as for flap vaginoplasty. If clitoral hypertrophy and genital ambiguity are present, the clitoroplasty and labioplasty are performed as for a low vaginal confluence. After the clitoroplasty is completed, the child is rotated prone and placed on chest and pelvis rolls. The child with a pure UGS and no ambiguity is initially placed prone.

The initial incisions are similar, and the perineal flap is developed. The UGS is exposed, and dissection is carried out in the midline. The rectum is retracted superiorly with a malleable retractor. We have found it helpful to split the UGS in the posterior midline well into the vagina. The malleable retractor is then placed in the vagina, and its posterior wall is retracted toward the rectum. This provides excellent exposure of the confluence of the anterior wall of the vagina and the urethra or bladder neck. Stay sutures are placed on the edges

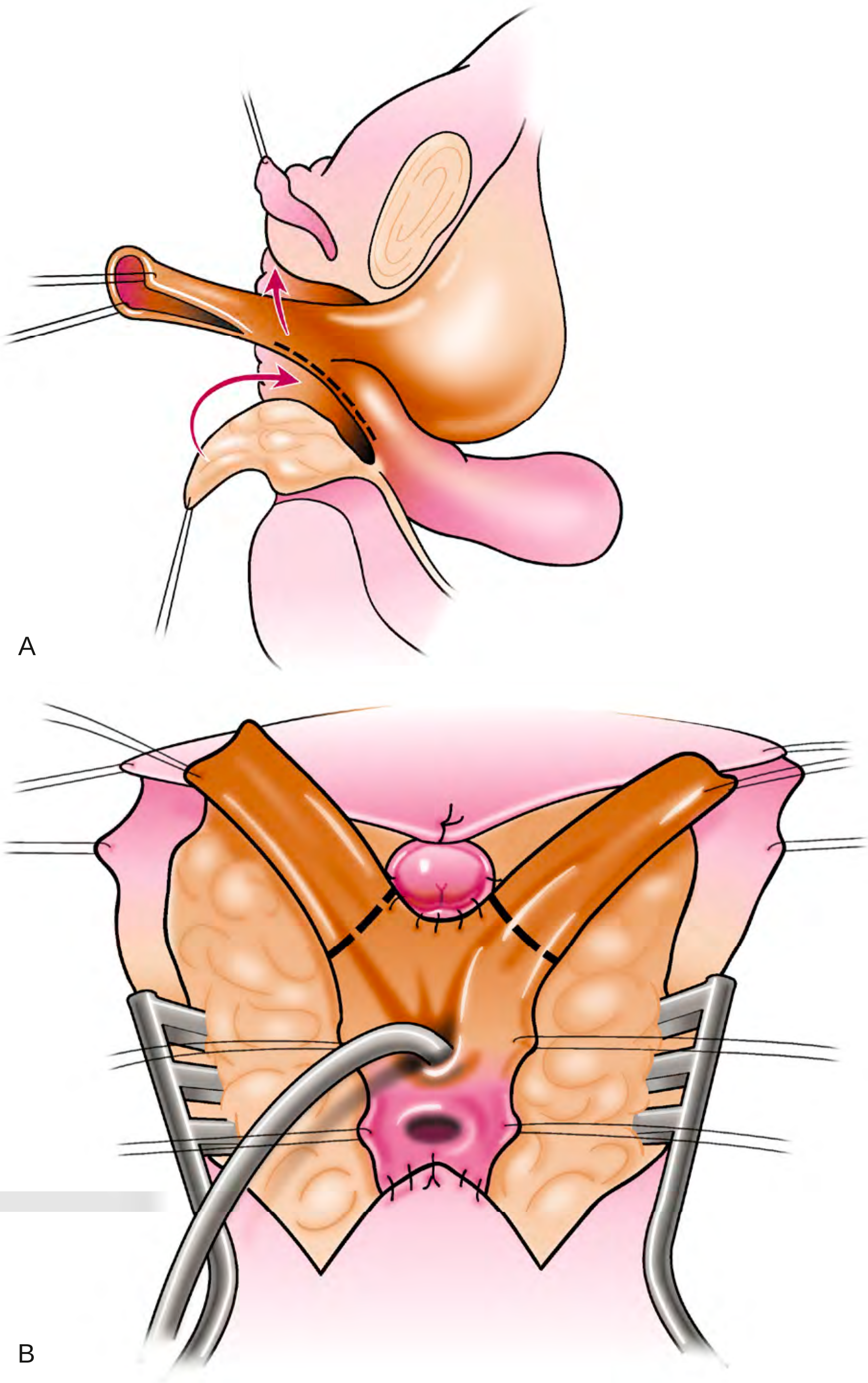

Figure 36-18 Use of excess sinus after TUM or PUM. Sinus may be split ventrally to create a mucosa-lined vestibule **(A** and **B),** dorsally to create a Passerini flap for the vaginoplasty **(C),** or laterally to complete the vaginoplasty **(D)**. The incised sinus is rotated in a spiral fashion to extend the vagina (**E** and **F**).

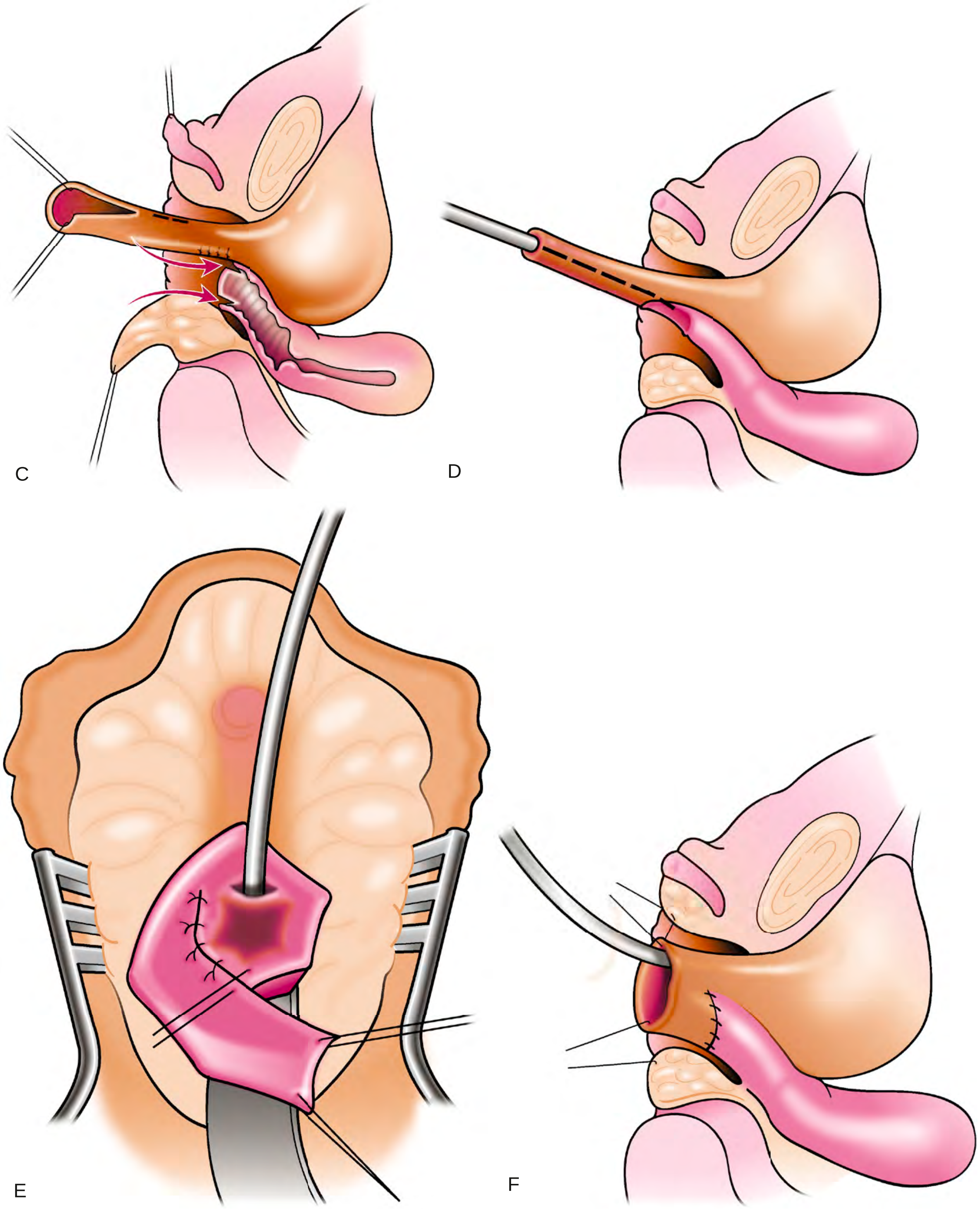

Figure 36-18, cont'd.

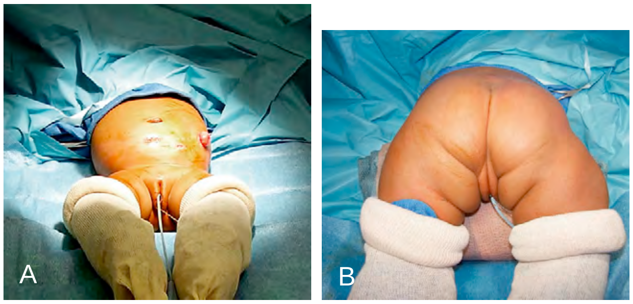

Figure 36-19 Total body preparation allows rotation of the patient from supine **(A)** to prone **(B)** position during the surgical procedure.

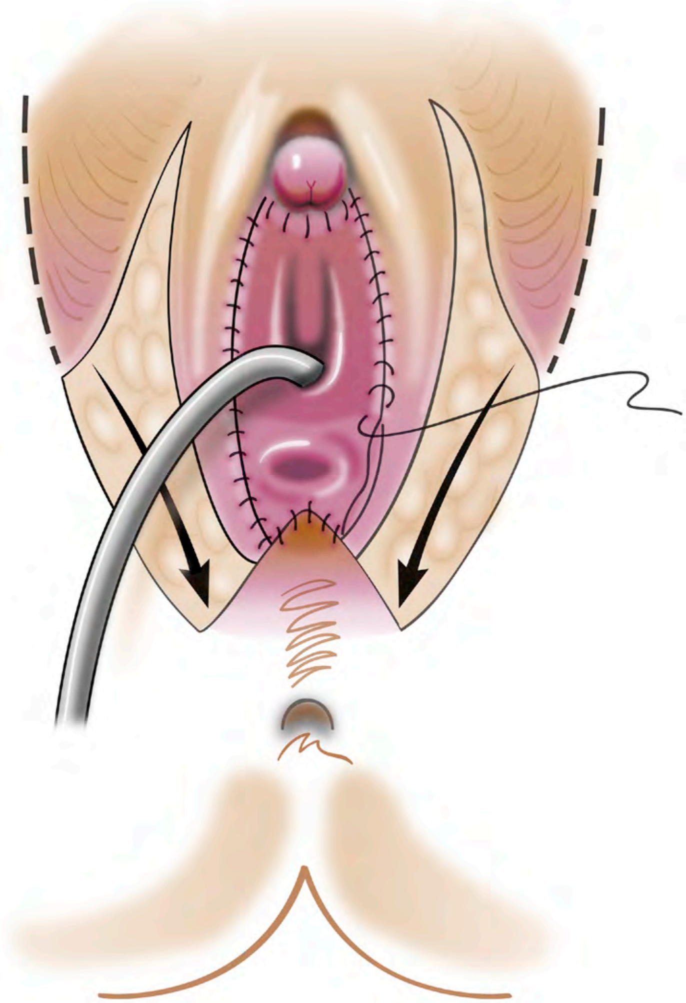

Figure 36-20 Labioplasty. The labia minora have been advanced beyond the vagina. The labia majora are mobilized inferiorly by YV-plasty.

of the vagina, and the anterior dissection is performed. The prone position allows excellent exposure. Even with good exposure, this dissection is tedious, because there is no true plane between the vagina and the urethra initially. The tissues may be quite thin as the dissection begins; the surgeon should err on the side of preserving the urethra and bladder neck tissue. As dissection extends proximally, the vaginal wall becomes thicker, and the dissection becomes easier.

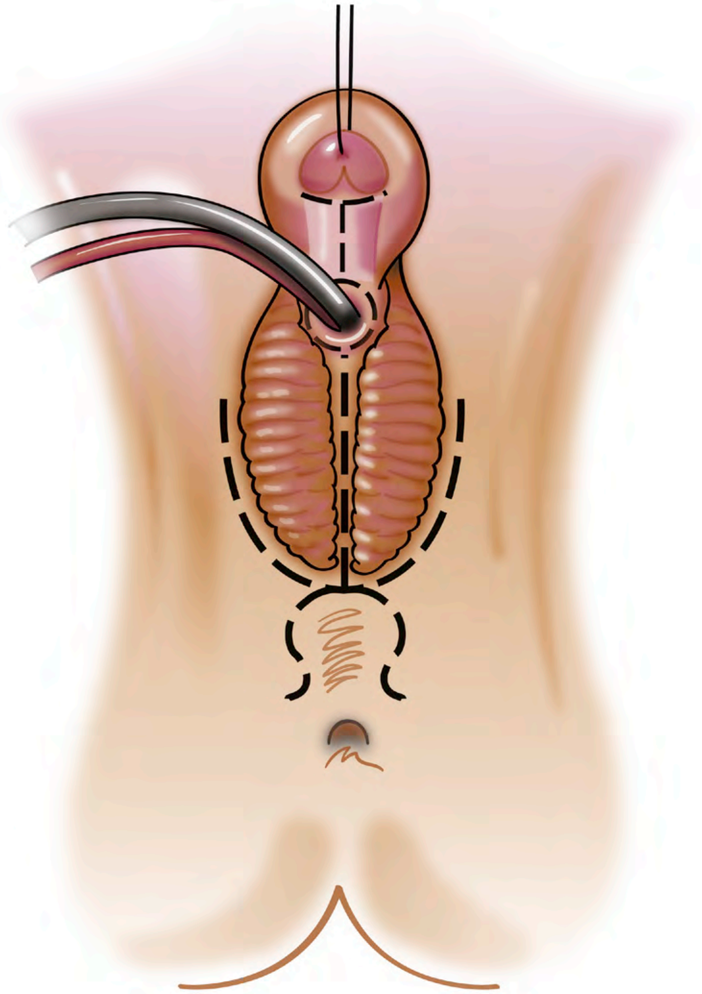

Figure 36-21 Incisions for total urogenital mobilization.

After the vagina has been adequately mobilized, the UGS is closed over a Foley catheter in at least two layers to create the urethra. If the vagina cannot be brought to the perineum, a preputial flap[98] or a buttock flap will be required to cover the neourethra and to create the anterior vaginal wall.[100] The child is now turned supine, and the perineal flap is sewn into the spatulated posterior vagina. A vaginal Penrose and Foley catheter are left indwelling.

TOTAL UROGENITAL MOBILIZATION AND PARTIAL UROGENITAL MOBILIZATION TECHNIQUES

The initial total body preparation, endoscopy, and catheter placement are as described earlier. If the child has an intersex condition with virilization of the external genitalia, the clitoroplasty and labioplasty are similar to the techniques described previously. In the TUM technique, the UGS meatus is circumscribed (Fig. 36-21) and multiple traction sutures are placed. If an enlarged clitoris is present but the meatus is on the perineum, the urethral plate is divided below the glans clitoris. The urethral plate is dissected off the corpora and mobilized in continuity with the UGS. Dissection begins in the midline posteriorly, and the attachments of the perineal and pelvic musculature between the UGS and rectum are divided. Care is taken not to injure the rectum or violate the spongy tissue of the sinus. Once this separation is completed, finger

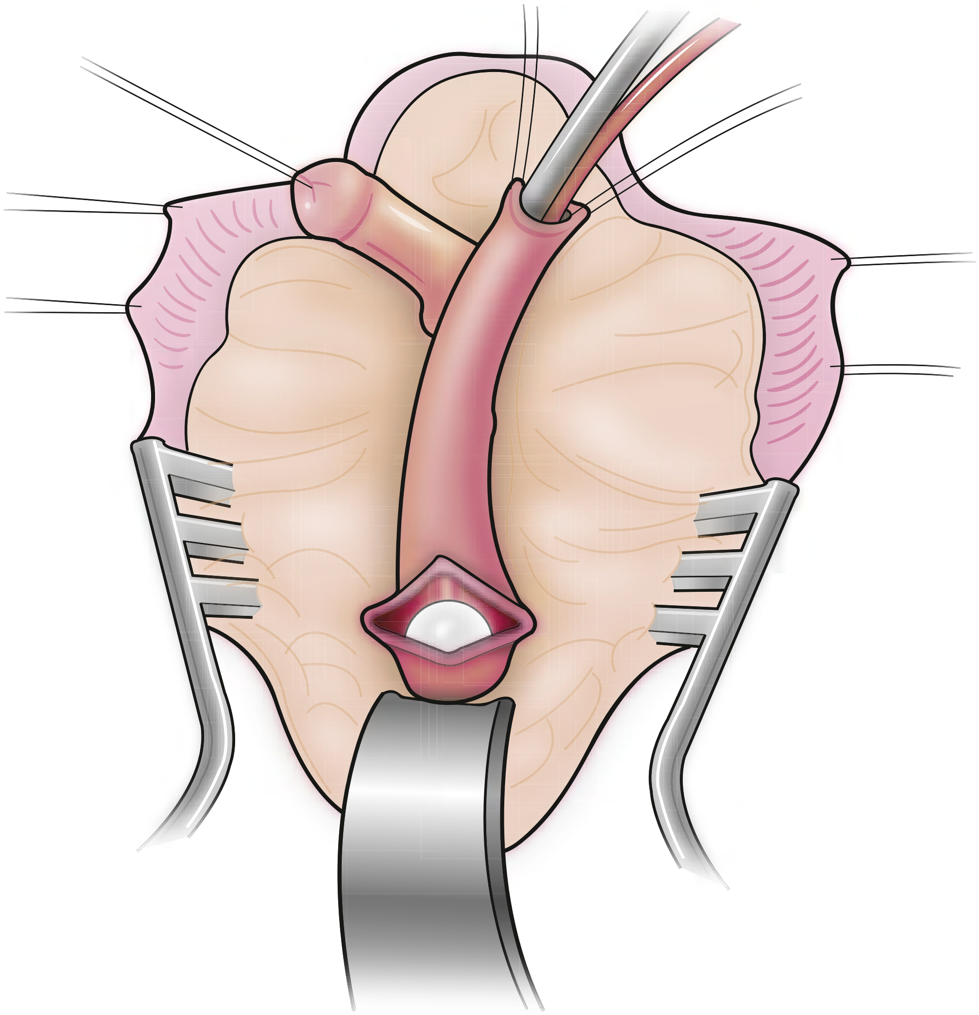

Figure 36-22 After urogenital mobilization, the vagina is opened over the Fogarty balloon.

dissection allows the entire posterior aspect of the vagina to be seen, and the peritoneum is swept superiorly. The sinus has been mobilized from the phallus to the pubis circumferentially. When the avascular ligaments from the pubis are divided, the sinus moves toward the perineum (see Fig. 36-17A). In PUM, the dissection stops at the pubourethral ligament (see Fig. 36-17B).

The Fogarty balloon in the vagina is now easily palpated. The posterior wall of the vagina is opened near the confluence (Fig. 36-22). If the vagina reaches the perineum, the UGS is opened ventrally and the redundant tissue is used to create a mucosa-lined vestibule (see Fig. 36-18A and B).[121] If the vagina is still too high, the patient is turned prone and the anterior wall of the vagina is separated from the urinary tract. The opening in the sinus is closed to create the urethra. The excess mobilized sinus in this situation is divided *dorsally* to create a Passerini flap for the anterior vaginal wall (see Fig. 36-18C). The patient is then turned supine, and the perineal flap is sewn into the spatulated posterior vaginal wall. If the sinus is opened laterally, the tissue can be rotated inferiorly to form the posterior wall of the vagina, minimizing the need for the perineal flap (see Fig. 36-18D).[121] Labioplasty is performed as previously described. A Penrose drain is left in the vagina, and a Foley catheter remains in the urethra.

Results of Urogenital Sinus Surgery

Reports of outcomes from clitoroplasty and vaginoplasty historically tended to focus on short-term cosmetic results rather than long-term functional results. Many surgeons question the validity of long-term results because the techniques have changed considerably over the past few decades. Nevertheless, it remains important to review the successes and failures.

From a cosmetic standpoint, the surgeon and parent are typically pleased with the feminized result. The primary cosmetic problem has been prominence of the glans clitoris. Alizai and coworkers[105] found an unsatisfactory cosmetic outcome from clitoroplasty in 46% of CAH patients. In an effort to determine functional results of clitoroplasty, Gearhart and colleagues[127] evaluated pudendal-evoked potentials and reported that nerve conduction was preserved. Others have demonstrated intact sensation after clitoroplasty,[87,88] but it is unknown whether this is a good indicator of healthy sexual function. Others have noted failure to achieve orgasm despite subjective sensation yet ability to achieve orgasm after radical clitoral resection.[92,128] Minto and associates[129] found inconsistent cosmetic results and evidence of clitoral tissue in women who underwent clitorectomy. A sexual satisfaction questionnaire identified avoidance and difficulty with sensuality and communication in these women, compared to nonoperated women, but both groups had orgasmic dysfunction. Given the complexity of factors contributing to normal sexual function, more prospective long-term studies are necessary to assess outcomes from contemporary techniques.

Published outcomes from vaginoplasty also must be interpreted with caution, because techniques have evolved significantly. Most surgeons who promote a single-stage feminizing genitoplasty in infancy concede that a secondary procedure may be necessary in a disappointing number of patients, but it is generally a smaller procedure with good results.[99] One group reported less need for a secondary procedure when vaginoplasty was completed early (3% versus 42% for delayed cases).[130] Parents should be counseled regarding the likelihood of another procedure at puberty. We do not recommend postoperative dilation programs in young children because of the psychological impact on the child and parents. Undergoing major genital surgery during tumultuous adolescence also could have a negative impact from a psychosocial and psychosexual standpoint, even if the procedure is desired. Those who advocate postpubertal vaginoplasty cite fewer secondary procedures despite the need to work with previously operated tissues.[106,131] Success may be related to pubertal tissue changes and willingness to accept home dilation.

Although early results from newer techniques such as TUM and PUM are encouraging, it will still be a number of years before a significant number of operated infants reach maturity. Until that time, concerns regarding incontinence and neural injury will remain. We also anticipate long-term results regarding sexual function and the need for revision surgery.

CLOACAL ANOMALIES

Evaluation

Although UGS anomalies can be very challenging problems, cloacal anomalies involve another order of complexity, because the rectum also enters the common channel. These disorders combine the most challenging aspects of both UGS and anorectal malformations. The internal and external anatomic anomalies occur on a wide spectrum. The genitalia may appear ambiguous and warrant an intersex evaluation. Other anomalies are common. These malformations occur in only 1 in 40,000 to 50,000 patients[132] and make up less than 15% of all anorectal malformations.[133] The evaluation is similar to that described for UGS abnormalities, but several important differences are noted here.

These children may be quite ill, with severe abdominal distention and ascites causing respiratory compromise. Cardiac malformations, renal abnormalities, and sacral anomalies are commonly present and should be addressed early.

History and Physical Examination

If the external anatomy appears ambiguous, a thorough intersex history is warranted. Even with the appearance of a phallic structure, children with cloacal malformations uniformly have 46,XX karyotype and ovaries.[134] Other children in the family with genital abnormalities or syndromes should be documented. The history is usually less revealing in this group, but any abnormal antenatal ultrasound studies should be discussed. Findings on prenatal ultrasound include hydronephrosis; a solitary, bilobed or even trilobed cystic mass between the rectum and the bladder, representing the distended vagina or vaginas; and ascites due to retrograde flow of urine through the genital tract.[135-141] Fetal MRI highlights these fluid-filled pelvic structures well.[141]

The physical examination is extremely important. The patient's overall appearance and any dysmorphic features should be noted. Clearance from a cardiac and pulmonary standpoint is important before any operative intervention; abnormalities of these systems are seen in 10% and 5% of cases, respectively.[142] The abdomen is often distended due to distention of the vagina, bladder, and colon. Hydrocolpos has been noted in 29% to 63% of cases.[143-146] The primary pathophysiology is vaginal voiding, although mucus may be trapped within an obstructed uterus or vagina. Hydrocolpos can result in sepsis and vaginal perforation, significant hydroureteronephrosis, urinary tract infection, and acidosis.[134] The hydrocolpos may also be severe enough to hinder venous return from the lower extremities.[147]

Because sacral anomalies are present in half of the cases,[148,149] the child should be turned prone to evaluate the back. Flattened buttocks suggest sacral agenesis, but any erythematous lesion, hair patch, dimple, or abnormal gluteal crease is suspicious for a bony sacral abnormality.

The genital examination should document the size, consistency, and length of any phallic structure and its relationship to the surrounding structures. We have seen a wide spectrum of external genitalia, including nearly normal presentations, various degrees of clitoral abnormalities, labial fusion, and even complete genital transposition (Fig. 36-23A and B). The single perineal orifice can also have a variety of appearances, resembling a vagina or a urethra, and may open on the perineum or on the phallus (see Fig. 36-23C). We and others have observed patients with an accessory urethral channel exiting the tip of the elongated clitoris.[132,150]

Other gastrointestinal anomalies, such as tracheoesophageal fistula, duodenal atresia, and rectal duplication, have been seen in children with a persistent cloaca.[132,150,151]

Radiographic and Endoscopic Evaluation

The radiographic evaluation of the child with a cloacal anomaly begins with a chest radiograph, a plain abdominal film, and abdominal and pelvic ultrasonography. The abdominal film may reveal a pelvic mass, and classic linear calcifications may be seen if urinary ascites has occurred. Granular calcifications along the course of the rectum represent calcified meconium from urine washing into the rectum.[152]

The abdominal sonogram will most likely reveal distention of the bladder, vagina, and rectum. Hydronephrosis is present in more than 50% of these newborns.[148,149,153] Hydronephrosis is usually caused by anterior displacement of the bladder outlet and ureteral compression, but true ureterovesical junction obstruction, ureteral ectopia, and ureteroceles have been reported. Renal ectopia, dysplasia, and agenesis are also found.[148,149]

Genitography is done as described for UGS anomalies, finishing with a formal VCUG if the urethra can be negotiated. Reflux is present in half of the cases.[148,149,154] Not only is the UGS more complex, with frequent vaginal duplication, but the rectal confluence must also be identified. The communication of the urinary tract, vagina, and rectum with the cloaca is quite variable. The urinary communication was found to be urethral in 77% of patients in one series, but in 23% it was at the bladder neck with essentially no urethra present. There was a single vagina in 43%, two vaginas were present in 44%, and no vagina was present in 13%.[153]

Endoscopically, we have found vaginal duplication in almost all of our patients, with the vaginas entering the cloaca side by side. They can enter anywhere from near the cloacal meatus to the bladder. One vagina may also enter the other. Hall and coworkers[155] found bicornuate

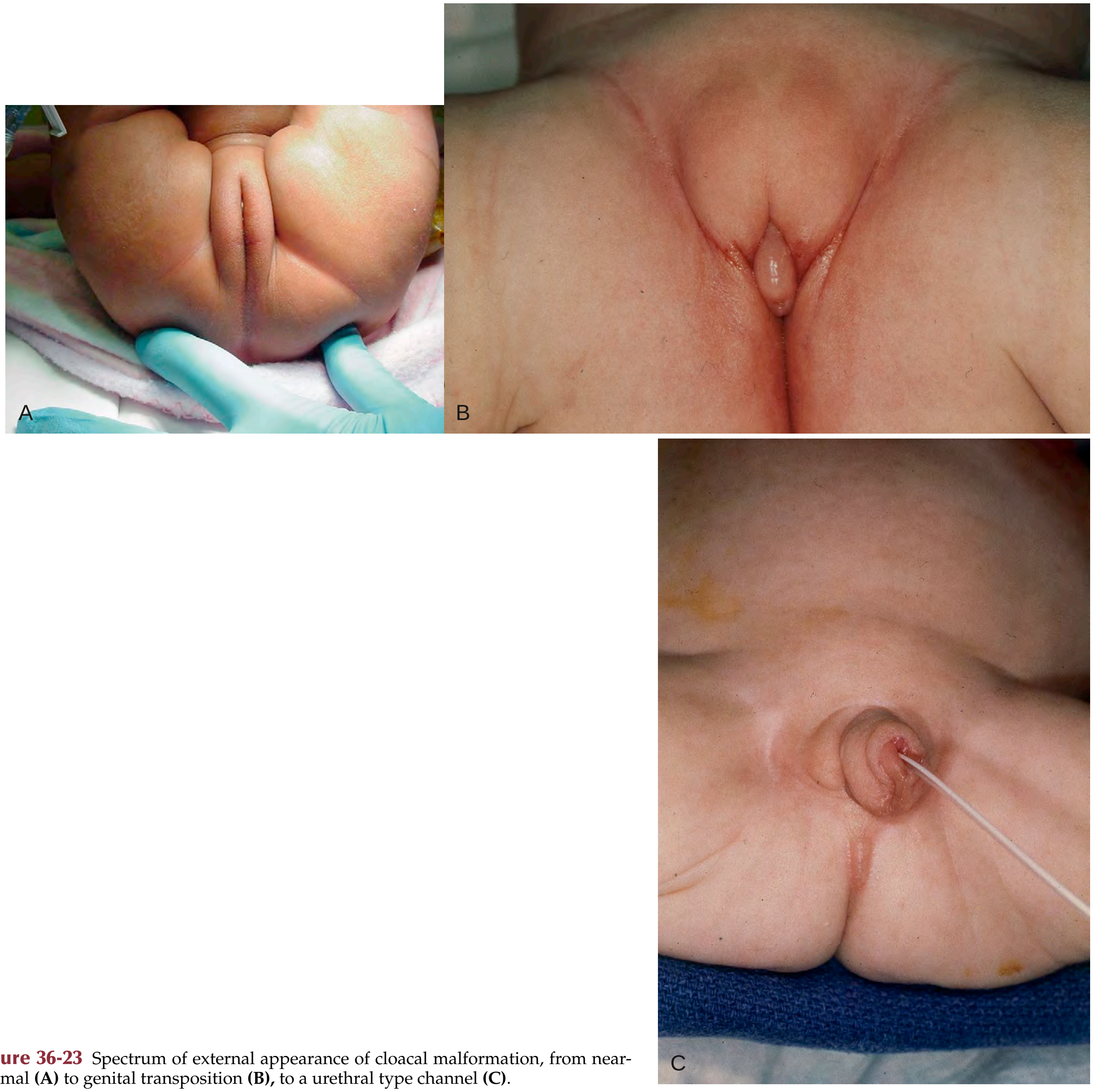

Figure 36-23 Spectrum of external appearance of cloacal malformation, from near-normal **(A)** to genital transposition **(B),** to a urethral type channel **(C)**.

uterus, hypoplastic uterus, or uterus didelphys in 35% of their patients. The rectal communication is also variable. The opening may be broad or narrow and can enter near the perineum, along the urethra, or in the bladder. No communication can be found in some patients. We have usually found the communication to be in the septum between the duplicate vaginal openings, but 11% of Hendren's patients had communication elsewhere.[153] We cared for one infant with distal atresia and no perineal opening in whom two cervices and the rectum entered the posterior wall of the bladder near the dome.

The initial evaluation is not complete until echocardiography and MRI of the pelvic anatomy and lower spine have been obtained. MRI has detected spinal abnormalities in up to 43%,[152] with spinal cord tethering in one third of patients.[153] MRI is also helpful to evaluate the sphincteric muscle development and the level of rectal atresia.[156]

Standard genitography may miss a duplicate vagina or may be difficult to interpret due to double densities. We have found three-dimensional magnetic resonance genitography to be helpful in appreciating the complexity of the anatomy for surgical planning.[157] Retrograde instillation of dilute gadolinium via the perineal orifice and antegrade via the mucus fistula fills the entire cloaca and demonstrates the vaginas and level of rectal atresia well, even after divided colostomy. This may be completed under the same anesthetic as MRI of the spine and pelvic floor.

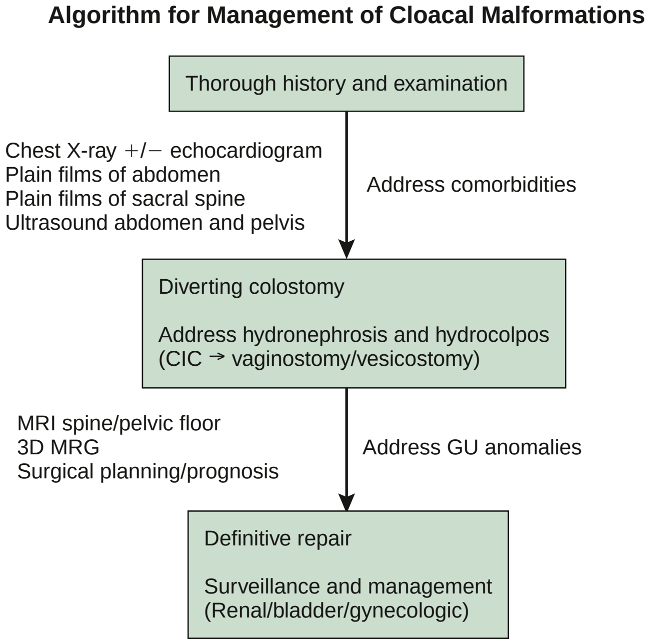
Algorithm for Management of Cloacal Malformations
Thorough history and examination
Chest X-ray +/− echocardiogram
Plain films of abdomen
Plain films of sacral spine
Ultrasound abdomen and pelvis
Address comorbidities
Diverting colostomy
Address hydronephrosis and hydrocolpos
(CIC → vaginostomy/vesicostomy)
MRI spine/pelvic floor
3D MRG
Surgical planning/prognosis
Address GU anomalies
Definitive repair
Surveillance and management
(Renal/bladder/gynecologic)

Figure 36-24 Algorithm for management of cloacal malformations. CIC, clean intermittent catheterization; GU, genitourinary; MRI, magnetic resonance imaging; 3D MRG, three-dimensional magnetic resonance genitography.

Surgical Reconstruction of Cloacal Anomalies

Initial Management

It is extremely important to medically stabilize the child born with a cloacal anomaly before considering any surgical intervention. These children are often quite ill with multiple anomalies. Abdominal distention secondary to vaginal and rectal distention is not uncommon and may lead to pulmonary compromise. The initial management involves decompression of the distended organs (Fig. 36-24). After satisfactory decompression, one must resist the temptation to do an isolated rectal pull-through. It is very clear now that definitive repair of all aspects of the cloaca should be addressed in the same sitting.[62,142,154,158,159] Although some have recommended delayed vaginoplasty,[155] this often requires remobilization of the rectum and necessitates working through previously scarred tissues. Hendren[158] was strongly opposed to staged repairs and noted that 60 of his 154 patients with cloacal anomalies had had prior surgical intervention. Peña and colleagues had similar concerns and a similar percentage of patients referred after failed repair.[154] The optimal age for repair has not been established and depends to a large extent on the other morbidities. Raffensberger initially proposed correction in the neonatal period,[147] but he later noted that this was not appropriate. Many choose 6 to 12 months of age for definitive cloacal repair, but the repair may be done safely in the neonatal period in otherwise healthy infants and in the most experienced hands.[154]

Surgical reconstruction of cloacal anomalies currently involves four steps: (1) decompression of the gastrointestinal tract, (2) decompression of the genitourinary tract, (3) definitive correction of any other urinary anomalies, and (4) repair of the cloacal anomaly.

A colostomy is performed promptly after delivery and stabilization of the child. This decompresses the gastrointestinal tract and prevents the flow of stool into the common cloaca. Hendren[160] recommended a right transverse divided colostomy, which allows ample bowel for both the rectal pull-through procedure and a potential bowel vaginoplasty. The left colic blood supply remains intact. However, leaving a large distal segment of colon allows an increased surface area for the exchange of urine electrolytes and may lead to dramatic hyperchloremic acidosis. Levitt and Peña recommended a divided colostomy just distal to the retroperitoneal attachment in the proximal descending colon and emphasized the importance of fixing the mobile colon to the abdominal wall to prevent prolapse.[134] If obstructed hydrocolpos is present radiographically and has not responded to catheterization of the cloaca, tube vaginostomy should be completed under this anesthetic.[134]

One should perform endoscopy at the time of colostomy, not only to define the cloacal anatomy but also to decompress the bladder and vagina and clear the distal colon of meconium and mucus. With initial endoscopy, the scope usually enters the vagina or vaginas. Draining the vagina further relieves abdominal distention and allows entrance into the urethra and bladder. Visualization of the lower urinary tract is often quite difficult at this age, because the bladder is compressed anteriorly toward the abdominal wall. The rectal fistula is usually located posteriorly in the septum between the duplicate vaginas, but can be located at almost any point from the cloacal meatus to the bladder. The scope is passed into the rectum or a catheter is passed through the abdominal mucus fistula, and the distal colonic segment is irrigated clear.

Narrow cloacas are more likely to result in vaginal and rectal voiding and may even lead to ascites antenatally.[139] If vaginal voiding continues, intermittent catheterization should be instituted. Although the catheter usually enters the vagina, it still provides adequate decompression.[160] Alternatively, the narrow channel can be opened a short distance distally to aid in voiding. If this is not successful, a cutaneous vesicostomy should be considered. We and others have found this to be useful without compromising later reconstruction.[142] Peña and associates firmly believe that vaginostomy should be performed before lower or upper urinary tract diversion is considered, because management of vaginal distention eliminates the source of urologic issues.[134,154]

The last component of therapy before definitive cloacal repair is correction of any obstructive or symptomatic urinary lesions and correction of other significant organ system problems such as cardiac or spinal cord defects.

Preparation and Repair

The patients receive antibiotic and mechanical bowel preparation with polyethylene glycol electrolyte solution (GoLYTELY). Definitive repair is performed by Peña's posterior sagittal anorectovaginourethroplasty (PSARVUP). Peña and coworkers noted that, in common channels longer than 3 cm, abdominal exploration is likely to be required, in addition to the posterior sagittal dissection.[154] Vaginal Fogarty catheters and a Foley bladder catheter are placed during endoscopy. It is also helpful to place a different-colored rectal Fogarty catheter. All are kept sterile as a thorough lower body povidone-iodine preparation is completed, as described earlier for the UGS repair. The child is then placed prone over chest and hip rolls, providing somewhat of a "jack-knife" position. With the use of an electrical stimulator, the area of maximal perineal contraction is identified as the location for the rectal pull-through. The initial incision and dissection is all done in the midline, from the coccyx to the posterior cloacal meatus. Although the catheters usually allow easy identification of the cloaca, it can be helpful to place a sound, as Hendren[150] proposed. As the sphincteric muscles are encountered and separated in the midline, they are marked with sutures. It can be helpful to open the cloaca in the midline posteriorly in its entirety to identify the various confluences, but this may not be necessary if TUM is to be done. The rectum is usually identified first and is divided from the common cloaca. Multiple sutures at the level of the fistula help in mobilization and later pull-through. Mobilization needs to be carried up to well above the sacrum, with separation from the peritoneum. Occasionally, abdominal exploration to provide further mobilization is necessary, and this change in positioning is allowed by the prior total-body preparation. The rectal sutures are used to retract the rectum from the genitourinary structures once mobilization has been completed.

In general, the repair of the remaining UGS is similar to a high UGS repair as described previously. This is most commonly addressed now with TUM. The repair is generally more difficult, because the vagina is usually duplex and often nearly surrounds the urethra. Differences from UGS repair alone are pointed out here.

The surgeon must be prepared for a wide range of vaginal anatomy. Side-by-side vaginal duplication has been present in most of our cases, and the septum can be divided with cautery at the time of endoscopy. If the vagina does not reach the perineum after TUM via a posterior sagittal and abdominal approach, the vagina is separated. Stay sutures on the vaginal confluence and upward retraction of the posterior vaginal wall are essential to aid in the difficult separation of the anterior vaginal wall from the urethra and bladder. The whitish color of the external vaginal wall is a helpful landmark to identify the proper vaginal plane. Often, the mobilized vagina reaches the perineum in a pull-through procedure similar to that for the rectum. If it will not reach, then several options are available for creation of a distal vagina. Small gaps may be bridged by labial or buttock skin flaps.[145,151] Larger gaps may be addressed by a vaginal flap, if the vagina is quite dilated, or by bowel interposition. Vaginal agenesis is addressed at this time by creating an intestinal vagina.

As in UGS repairs, the opening or openings in the UGS are next closed in two to three layers to create a urethra. The vagina is sutured to the perineum inferior to the urethral meatus. A perineal body is constructed, and the rectum is placed posterior in the previously marked area of maximal contraction. The dilated rectum may require tailoring to allow the rectum to be placed anterior to the sphincteric musculature.

Postoperative care is critical. The urethral catheter is left indwelling, and endoscopy is done in 3 weeks to assess the urethra, vagina, and rectum. Rectal dilation is begun at this time, and the colostomy is closed in 3 months. It is imperative to identify any voiding abnormalities early on, because a neuropathic component is present in at least one third of patients. Upper tract changes and even loss of renal function have been seen if abnormal voiding dynamics are not appreciated. Urodynamic studies should be performed, and clean intermittent catheterization (CIC) should be initiated if poor emptying is noted.

Peña's TUM appears to be a major advance in cloacal reconstruction. Circumferential mobilization of the urogenital component is performed after rectal separation. This allows the entire sinus to be moved down toward the perineum and may prevent the need for vaginal separation. If separation remains necessary for a pull-through vaginoplasty, it is still more easily performed.[100]

Outcomes

Although repair is technically demanding, the reported results have been satisfactory, particularly when one recognizes that many cases potentially have a neuropathic component. An abnormal sacrum has been noted in roughly 50% of cases.[148,149] In Hendren's experience, 59% of patients voided spontaneously with control, and 28% required CIC.[153] The remainder were either not mature enough to characterize or had urinary diversion. In his initial series, Peña[145] recognized that continence was related to the status of the sacrum: 73% of those with a normal sacrum were continent, compared to 29% of those with an abnormal sacrum. In the updated 2004 series of 339 children, continence data were stratified by length of the common channel. Spontaneous continence with voiding was present in 54% of patients, and the remainder were dry on CIC. The rate of CIC was lower in those with a common channel shorter than 3 cm in length (28% versus 78%).[154] In the Indiana experience, 86% achieved continence, but only one third were able to do so without CIC.[148]

Although the utility of TUM in complex reconstruction is clear, there has been concern regarding the impact of high circumferential dissection on the peripheral pelvic plexus nerves. Warne and associates[161] prospectively assessed urodynamic function in infants with cloacal and anorectal malformations undergoing reconstruction. Ninety percent of infants with cloacal malformations had abnormal urodynamics at baseline, most commonly neurogenic detrusor overactivity, and 50% showed deterioration after TUM. Those with a long common channel (>3 cm) were most at risk. The most common finding was inadequate detrusor activity and increased bladder capacity. Although the sparse pelvic plexus in children with sacral anomalies may be more vulnerable to iatrogenic injury, this urodynamic pattern was not typical of the anorectal malformation cohort who underwent posterior sagittal dissection, nor of a historical cohort of cloacal malformations who had reconstruction before the introduction of TUM. Peña and colleagues noted that the typical urodynamic pattern is hypocontractile.[154]

Kryger and González[162] did not see impaired continence after TUM for UGS, but formal urodynamic evaluation was not performed, and the likelihood of baseline neurologic impairment in this group would be low. In Peña and coworkers' experience, the rate of continence with voiding was the same in the cohort who had TUM as in the cohort who had the traditional posterior sagittal approach (58% versus 60%).[154] The Great Ormond Street group reported 68% continence after TUM in 22 patients, with 47% voiding and 53% requiring CIC. Two of the CIC patients had also received bladder augmentation due to poor bladder compliance. Twenty-three percent were too young to determine continence.[163]

It is important to remember that the long-term renal prognosis is affected by the baseline renal reserve, coexistent congenital urologic anomalies, and long-term management of bladder dysfunction. Vesicoureteral reflux is present in approximately 50% of newborns with cloacal malformations.[148,164] Warne and associates[164] reported chronic renal failure (creatinine clearance <80 mL/min/1.73 m^2) in 50% of patients, with 17% progressing to end-stage renal disease. Baseline dysplasia, solitary kidney, vesicoureteral reflux, and sacral anomalies were risk factors for chronic renal failure. Nadir creatinine concentration during infancy did not appear to have the same prognostic value as in patients with posterior urethral valves.[148]

Fecal continence is similarly affected by neurologic status. Hendren[160] noted good prognostic features for fecal continence: a well-defined gluteal cleft and anal dimple, absence of sacral anomalies, normal MRI, and brisk reflexes. Of 105 patients, 47 had normal bowel function, 27 used enemas, 7 had a colostomy, and 7 had fecal soiling. Among Peña's patients,[145] 18 of 19 with a normal sacrum had voluntary bowel movements, but many required a bowel program to be clean. Fewer than half of those with an abnormal sacrum had voluntary bowel movements. In his and associates' updated series,[154] 60%

had voluntary bowel movements, but two thirds had some soiling. Forty percent were incontinent but clean on a bowel program.[154] In the Great Ormond Street experience, 55% of those who were old enough for continence achieved voluntary bowel movements; one third of them required antegrade enemas. There was no difference in continence based on length of the common channel.[163]

Gynecologic outcomes are just beginning to become clear as these series of children reach puberty. Hendren[153] noted that 17 of 24 adults in his series had had intercourse, and 6 had had children. In 1998, Levitt and associates[165] detailed the gynecologic situation of 22 pubertal girls with repaired cloaca. Several had known atretic uterine structures that were removed during initial reconstruction. Nine patients presented after puberty with a palpable abdominal mass, with or without cyclic pain, caused by retained or retrograde menstruation. The level of atresia varied, and, although renal anomalies were common, there was no correlation of laterality between renal and gynecologic anomalies. This group later recommended verifying the patency of the female genital tract by cannulating the fallopian tube and injecting with saline.[154] Warne and associates[166] found functioning uterine tissue in 68% of young women at puberty. Roughly half of these had normal menses, and the others had retained menses. Vigilance at the time of puberty, with or without abdominopelvic imaging, seems prudent.

CONCLUSION

Abnormalities of the female genitalia range from straightforward and easily managed cases to extremely complex, life-threatening anomalies. External genital anomalies, particularly those resulting in some degree of ambiguity, cause significant parental anxiety necessitating prompt evaluation and great compassion. Information should be disclosed to the parents as it becomes known, empowering them to participate in decision making. Controversy continues to surround the role of surgery in children with disorders of sex development, a situation that should improve as providers embrace the consensus guidelines for a team approach and long-term support. At this point, we have a lot to learn from the experiences and outcomes of affected individuals. It is important to remember that “normalizing” the genitalia does not cure a disorder of sex development and that parents and patients deserve some autonomy in these important decisions.

The operative approach to clitoromegaly, UGS, and cloacal malformations has gradually evolved, and attempts are now made to ensure not only feminine cosmesis but also normal functional results. Repair of the most complex anomalies remains technically demanding, and the surgeon must be prepared for both intraoperative challenges and lifelong surveillance of renal and gynecologic outcomes.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 37

ADOLESCENT UROGYNECOLOGY

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Adolescent urogynecology continues to be an area of great change and controversy. Advances in medical treatment mean that many more children are surviving into adolescence and adulthood who may not have done so before. In children with major congenital anomalies such as cloacal anomalies, childhood surgery in the past concentrated purely on renal and gastrointestinal problems. It is only with the onset of adolescence that issues such as sexual function and fertility become more relevant. Treatment options for all adolescents are improving, and there is a wider range of treatment possibilities available now.

Adolescence is a transitional time for all patients, who will become more involved in their own care. They will wish to know more about their own conditions and to have a much greater input into decision making about their treatment. The advent of well-run support groups, such as those for androgen insensitivity syndrome (AIS) and congenital adrenal hyperplasia (CAH), has begun to improve the quality of care offered to these patients. Support groups facilitate two-way transmission of information between patients and physicians that can only be of benefit to both. Patients are more aware of the treatment options available to them and how to access them. They can be more fully involved in decisions, and, in the long term, a greater equity of care should be achieved.

However, because of all these changes, it is imperative that we offer as much evidence-based information as possible about various treatment options. This allows patients and their physicians together to make decisions that are often complex. However, as this chapter demonstrates, there are still few good data available. Long-term follow-up studies are often impaired by the fact that, on reaching late adolescence, patients are transferred to an adult unit. Pediatric surgeons may not then have access to information on the long-term outcome of genital surgery performed on their patients during childhood. Suitability (or otherwise) for sexual function may not yet have been ascertained.

At present, we are unable to answer many of patients' most basic questions regarding long-term follow-up. It is also becoming clearer, as we do obtain long-term data, that the results of surgery are often unsatisfactory. The evidence may eventually challenge preexisting widely held tenets regarding the timing and nature of childhood genital surgery.

VAGINAL ANOMALIES

The vagina can be absent entirely or shortened. This may occur as an isolated abnormality or as part of a recognized disorder of sexual development such as AIS. Vaginal agenesis is usually associated with an absent or poorly developed uterus. It can also occur together with complex pelvic anomalies such as cloacal exstrophy and anorectal agenesis (Fig. 37-1). Patients can present during childhood, particularly if their vaginal absence is part of a complex condition. Vaginal agenesis can also be diagnosed in an adolescent who presents with primary amenorrhea. If a uterus is present but the vagina is absent, atretic, or imperforate, nondrainage of menstrual loss can cause urgent presentation and serious sequelae.

The vagina is also affected in CAH, in which the main clinical features are clitoromegaly and fusion of the lower vagina and labia. Current management is to perform a feminizing genitoplasty in early childhood, as described in Chapter 36. The vagina may be inadequate for sexual intercourse in later life and will need further assessment and probable further surgery in adolescence.

CAUSES OF VAGINAL ABSENCE

Androgen Insensitivity Syndrome

AIS results from an abnormality of the androgen receptor. In the fetus with AIS, testes form normally due to the action of the SRY gene. They produce both testosterone and anti-müllerian hormone (AMH). Because AMH causes regression of the müllerian system, the fetus will not develop a uterus or upper vagina. In complete androgen insensitivity syndrome (CAIS), the androgen receptor is unable to respond, the external genitalia do not virilize, and the external appearance is female. Gender identity is usually female with the uterus being absent and testes present at some point along the line of descent from the abdomen to inguinal canal.[1] In partial androgen insensitivity syndrome (PAIS), there seems to be some response of the androgen receptors and the external genitalia virilize to some extent. There is a wide spectrum of physical presentation. However, in both types of AIS, the vagina is blind-ending and usually shortened. The length of the vagina is variable; it may be just a skin dimple, or it may be several centimeters long. In children with PAIS, reconstructive surgery is usually initiated during childhood to feminize the external appearance of the clitoris and vagina. In CAIS, treatment of the vaginal hypoplasia should be deferred until adolescence. Full disclosure of the diagnosis, including karyotype, is recommended, and psychological counseling and peer support are essential. Initial treatment for the shortened vagina is with vaginal dilators before reconstructive surgery should be considered.

Mayer-Rokitansky-Küster-Hauser Syndrome

Mayer-Rokitansky-Küster-Hauser syndrome is a rare condition, with an estimated incidence of 1 in 20,000 females. The most common presentation is with primary amenorrhea. The external genitalia and pubertal development are normal. The vagina and uterus are absent, and the diagnosis is made on ultrasonography and magnetic resonance imaging. Laparoscopy is rarely necessary. Occasionally, the uterus exists as very rudimentary horns lying on either side of the pelvic wall. Further investigations reveal a normal female karyotype and normal ovarian function. The cause of this condition is not yet known, although familial cases have been described. Up to 40% of these women also have urinary tract malformations, which may be minor or significant. In addition, skeletal anomalies are present in up to 12%.

As with AIS, the patient is not able to menstruate or to carry a pregnancy. Initial management should be geared toward exploring and trying to come to terms with the diagnosis. The vagina is often short, and further intervention is usually

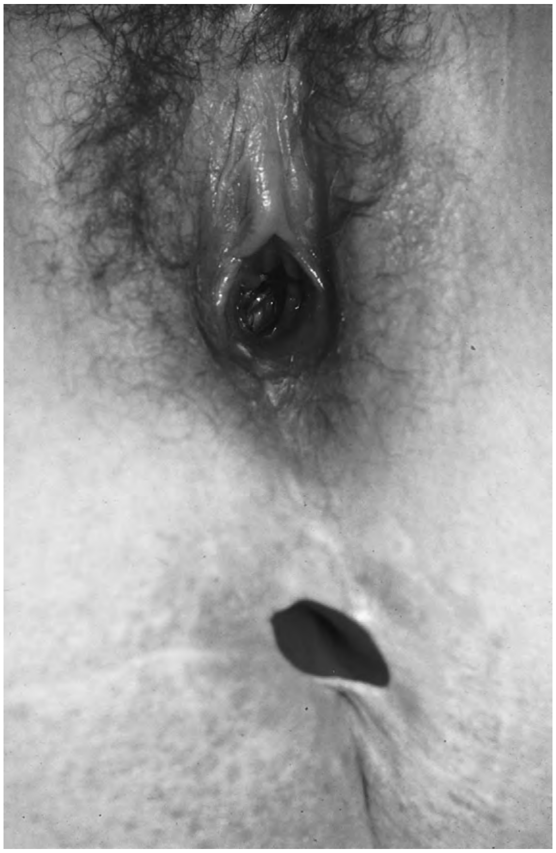

Figure 37-1 A 14-year-old girl with a cloacal anomaly and multiple complex surgeries. The anterior opening is a reconstructed urethra. The posterior opening is an anal pull-through. Both are no longer used because she has a urinary diversion and ileostomy. She has no vaginal opening at all and presented with cyclic abdominal pain and an abdominopelvic mass. A diagnosis of hematometria was made.

necessary before a normal sex life is possible. The use of vaginal dilators is the first line of management, before surgical options are considered. Because ovarian function is normal, some women choose to explore the options of surrogacy, despite the financial and emotional difficulties of this approach.

TREATMENT OF VAGINAL AGENESIS

Nonsurgical Treatment

Vaginal dilators were first used in the treatment of vaginal agenesis in 1938. Frank[2] described the use of graduated glass dilators as a nonsurgical technique to produce an artificial vagina. Since its description, this has remained the technique of first choice. The daily repeated insertion of graduated dilators over a period of several months allows development of a vagina. The technique is to apply gentle pressure and to use the dilators regularly for 30 minutes two or three times a day. Once the vagina is capacious enough to allow intercourse, the dilators can be discontinued, because intercourse itself will stretch the vagina. The main key to success is the motivation of the patient, and retrospective success rates of 78% having “normal sexual function” have been reported.[3] However, some women find dilator treatment difficult and distressing.[4] Methods to try to improve compliance, such as use of commercially available sex aids, have been tried with some success. Failure with dilators leads to the consideration of surgical methods.

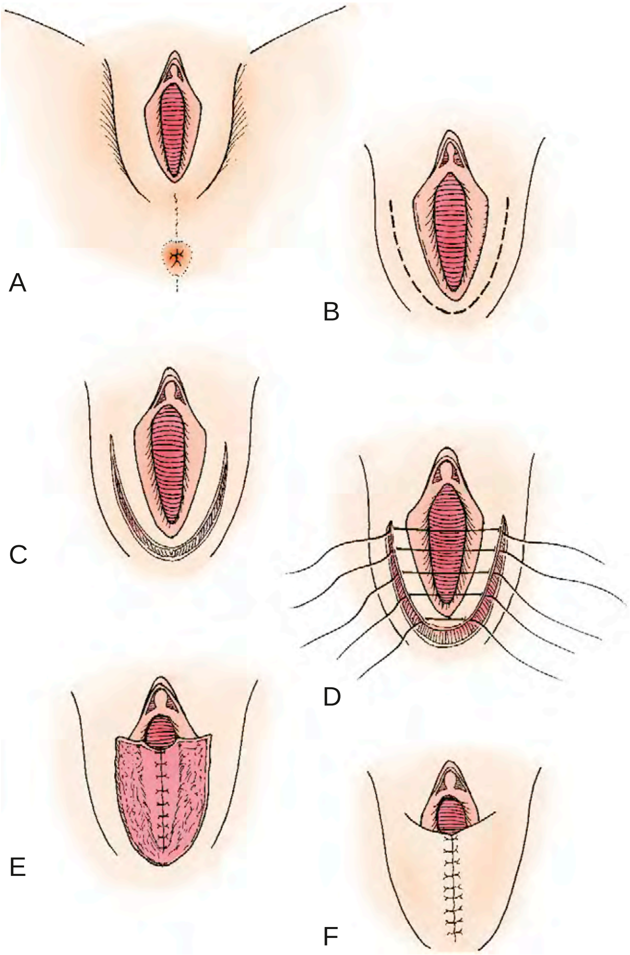

Figure 37-2 Williams vulvovaginoplasty. **A,** Before surgery. **B,** Incision. **C,** Dissection. **D** and **E,** Sutures. **F,** Final result.

Surgical Treatment

Surgical intervention is indicated if vaginal dilators have been unsuccessful. Patients without previous surgery achieve the best results with dilation. Those patients with previous pelvic surgery causing scarring of the genital area often require surgery as a first choice, because dilators are ineffective.

Williams Vulvovaginoplasty

The Williams vulvovaginoplasty procedure was described in 1964[5] but is rarely used nowadays. The labia majora are used to make a tubular horizontal vagina, which is essentially external to the body (Fig. 37-2). The surgery is simple and relatively noninvasive and may be most suitable for those patients in whom dissection to form a neovagina is impossible. Satisfactory results have been reported.[6] However, the vagina may still be short, and the fact that it is external may mean there is no real feeling of penetration during intercourse. It is possible that it allows for better clitoral stimulation.

Vecchietti Technique

The Vecchietti technique combines elements of surgery and vaginal dilation. The technique relies on the principle of continuous pressure to form a vagina. The pressure is applied by an acrylic olive placed at the vaginal dimple. Threads from the olive are passed through the potential neovaginal space through the abdominal wall and connected to a traction device. The device is tightened over a period of 8 to 10 days. Recent modifications include performing the procedure laparoscopically, thereby avoiding a laparotomy and prolonged hospital stay.[7,8] Reported success rates are high, although series have been small and no long-term follow-up data are available yet.

Creation of Neovagina and Lining with Various Tissues

SPLIT SKIN GRAFT

The split skin graft is probably the most widely used technique worldwide; it was initially described by Abbe[9] and later by McIndoe and Bannister.[10] An H-shaped incision is made over the vaginal dimple. Dissection is then performed between the bladder and the rectum to form a neovagina. Morbidity is low because the dissection is all extraperitoneal, although care must be taken with the angle of dissection to avoid damage to adjacent organs. A median raphe of tissue may be encountered and must be divided. The next step is to line the cavity, and in the original description this was done with a split skin graft. The skin graft is sutured or glued to a vaginal mold and placed in the vagina. The cavity must then be kept open by a soft, silicone-covered foam mold, which is sutured into place. The mold is changed with the patient under general anesthesia 1 week after the original surgery. It is then left in place for 6 weeks, except for cleaning. Once the mold is removed after 6 weeks, the patient will need to use vaginal dilators regularly. The duration of dilator use is not clear, but because contracture is a major complication, dilators should probably be used indefinitely unless replaced by regular intercourse. Complications include contraction of the graft and dyspareunia. The vagina may also be dry and require lubrication. The neovagina is at risk of premalignant and malignant change, and these have both been described.[11]

AMNION

Other tissues, such as amnion, have been used to line the neovagina.[12] Amnion can be obtained at elective cesarean section and avoids the disadvantage of scarring at the donor site, although dyspareunia is a problem. However, amnion donation is controversial and complicated to organize. Because of the risk of infection, the collected amnion should be frozen and stored. It is then cultured and, if sterile, can be used. Because the practical logistics of amnion donation are considerable, this technique is rarely used nowadays.

PERITONEUM

Davydov[13] first described the use of peritoneum to line the neovagina. A neovaginal space is created as in the McIndoe procedure, and then an abdominal approach is used to free a cylinder of peritoneum and bring it down to line the neovagina. The top end of the vagina is then closed by suturing bowel, usually colon, across it for a vaginal roof. This procedure can now be performed laparoscopically and is suitable for patients in whom previous surgical scarring prevents dilation or the Vecchietti procedure.[14]

Intestinal Transposition

Different parts of the intestine in varying surgical modifications have been used as vaginal replacement. Baldwin, in 1904, used a loop of ileum.[15] The complications surrounding the first few cases included death, and this led to the procedure's being abandoned for almost 60 years. Pratt[16] modified the operation and used sigmoid colon with success. Cecum and ileum have both been used to replace the vagina. All bowel segment vaginoplasties require an abdominal and perineal approach, and a loop of bowel is brought down while its blood supply is retained. The distal end is sutured to the introitus, and the proximal end is closed. Gut continuity is restored. This type of surgery is indicated for patients who have undergone extensive pelvic surgery and in whom dissection to form a neovagina by any other means is impossible. This includes patients with major pelvic anomalies such as cloacal exstrophy as well as those who have failed with other methods such as McIndoe procedures.

The major advantage of this procedure is that contracture does not occur and dryness is not a problem. A good length of vagina can be achieved. The patients do need to douche regularly, because mucous discharge is a persistent and sometimes distressing problem. The vagina can prolapse outward and can have an unsightly "stoma-like" appearance. Symptomatic diversion colitis may occur and raises concerns about the use of colovaginoplasty in children.[17] Adenocarcinoma of bowel segment vaginoplasties has also been reported.[18]

CLITORAL HYPERTROPHY

The most common cause of clitoral hypertrophy in XX females is CAH. The 21-hydroxylase deficiency accounts for about 90% of cases.[19] Presentation is usually at birth, although patients with mild disorders caused by decreased enzyme activity rather than enzyme deficiency can present in the peripubertal period with premature adrenarche and hirsutism. Clitoral hypertrophy can also occur in rarer conditions, including maternal ingestion of androgens or progestins during pregnancy. Androgen-secreting tumors can also cause virilization. They are rare and include arrhenoblastomas and pregnancy luteomas.

Clitoral hypertrophy is also a feature of incomplete AIS. The etiology of incomplete AIS is similar to that of CAIS, although the genitalia are partially responsive to the effects of testosterone in utero. This gives rise to a spectrum of clinical features ranging from a slightly virilized female appearance to normal male anatomy with impaired spermatogenesis or impaired virilization at puberty or both. Several classifications have been proposed.[20] If the gender of rearing is female, surgery is most frequently performed in childhood but may need later revision.

Testosterone biosynthetic defects also lead to ambiguous genitalia. These include conditions such as 5α-reductase deficiency, in which mutations in the gene for 5α-reductase type II isoenzyme lead to disruption of sexual development in utero. Children are usually born with ambiguous genitalia and reared as female. At puberty, virilization occurs, causing growth of the phallus and sometimes descent of the testes into the scrotum (Fig. 37-3). Several populations around the world with a higher prevalence of this disorder have been described, including the Dominican Republic,[21] Papua New Guinea,[22] and Turkey.[23] Successful change into the male gender has been described in large cohorts of affected patients, and some have fathered children.[24] However, some affected patients prefer to remain female and may request surgical intervention.

Other defects anywhere within the biosynthetic pathway from cholesterol to dehydroepiandrosterone will cause a defect in testosterone production. Patients present with variable degrees of genital ambiguity. The most common block in testosterone biosynthesis affects 17-ketosteroid reductase (also called 17β-hydroxysteroid). Presentation at birth is similar to that of PAIS. Surprisingly, these women do show signs

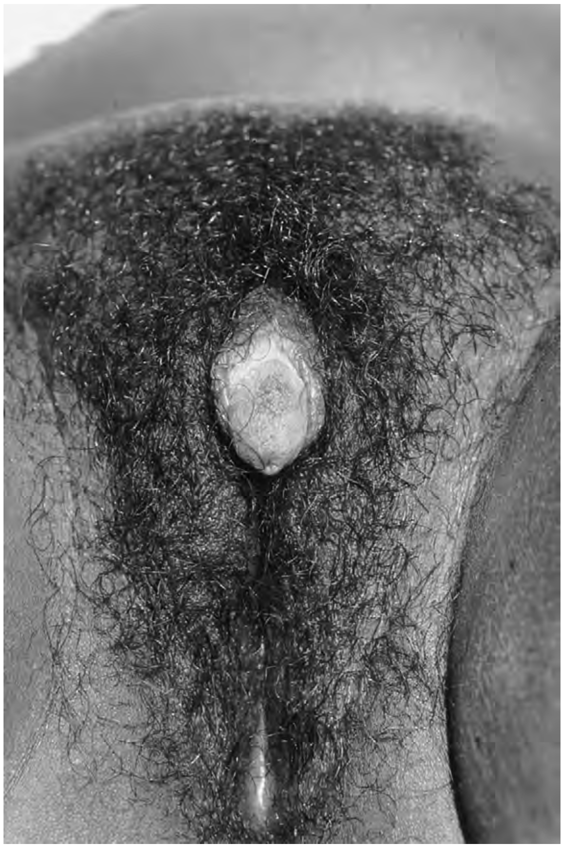

Figure 37-3 A 16-year-old XY female with 5α-reductase deficiency before clitoral reduction.

of virilization at puberty, and the mechanism is unknown. A proportion of affected women opt to change gender assignment at puberty.

Surgery of the Clitoris

Clitoral Reduction

Clitoral reduction is commonly performed as part of a genitoplasty in early childhood. Although this surgery is planned to be definitive, many patients with CAH require further clitoral reduction, possibly because of poor steroid control that allows a persisting androgen stimulus. Symptoms are reported to include painful erections and awareness of a "swelling" in the clitoral region.

Types of Surgery

Several surgical techniques have been described. Clitorectomy (removal of the whole clitoris) was used in the past but is not now an acceptable option. The clitoris is recognized as an important sensory organ involved in sexual response. Later, surgeons aimed to preserve as much of the enlarged clitoris as possible and buried the corpora under the skin.[25] However, this meant that the erectile tissue was concertinaed under the skin and, when erect, was very painful. Further modifications of the technique described excision of corporal tissue and preservation of the glans and the neurovascular bundle to reduce any loss of sensation.[26,27] Gearhart and colleagues[28] performed pudendal evoked potentials during feminizing genitoplasty on six young children. They demonstrated preservation of nerve conduction and suggested that this may permit normal sexual function in adulthood. Long-term follow-up of these children will not be available for many years. However, adult patients who underwent genitoplasty as children were shown to retain normal pudendum-evoked potentials but still had impaired sensation and orgasmic response.[29]

DUPLICATION ANOMALIES

Duplication anomalies arise from failure at some point of the fusion of the paired müllerian ducts. The true incidence of such anomalies is unknown, because many are entirely asymptomatic and found by chance. The incidence is higher in women with infertility and recurrent miscarriage. Uterine anomalies can be isolated but are also associated with an increased incidence of renal anomalies. Uterine anomalies, in particular duplication, are very common in girls with cloacal anomalies. Diethylstilbestrol exposure also leads to an increased risk of müllerian anomalies.

Vaginal Duplication

Management of duplication anomalies depends on the type of anomaly and the symptoms. A longitudinal vaginal septum can cause painful intercourse. This condition is usually diagnosed on examination, because it can be missed on ultrasonography. Resection of the septum is straightforward and curative. Vaginal duplication is, however, often associated with a double uterus and cervix.

Uterine Duplication

A double uterus is not usually an indication for surgery. Successful pregnancy can occur, and surgery to remove one uterus may compromise the remaining uterus. However, in some cases, there is a bicornuate or septate uterus, which may possess a noncommunicating uterine horn. In this situation, when menstruation starts, the noncommunicating horn will fill with blood, resulting in a hematometra. This causes severe dysmenorrhea and is also associated with an increased incidence of endometriosis. If the communicating uterus is of an adequate size, resection of the obstructed horn is the treatment of choice and can be done laparoscopically. If both horns are very small, a metroplasty may be considered to unite them. The Strassmann procedure has been used in treatment of a bicornuate uterus. In this procedure, a transverse incision is made exposing both cornu. The septum is excised, and the uteri are reunited. The Tompkins procedure involves a vertical incision in the back of the uterus over the septum. The septum is removed, and the cavity is closed without loss of space; this is most suitable for a septate uterus. If the septum is thin and easily visualized hysteroscopically, then hysteroscopic resection is possible, and this procedure is increasingly used.

Transverse Vaginal Septum

Transverse vaginal septum can be an isolated finding or associated with other anomalies. Presentation is with primary amenorrhea and cyclic abdominal pain. The condition must be differentiated from an imperforate hymen, which has similar symptoms. Imperforate hymen is easily diagnosed by a bluish bulge at the vagina, and simple surgical drainage is curative. With a transverse vaginal septum, the septum can be thick and treatment difficult. The approach to surgery depends on the position and thickness of the septum, and this can be determined by ultrasonography and magnetic resonance imaging if necessary. If the septum is in the lower third of the vagina, blind dissection may be adequate to reach the hematometra and drain it. The septum is then excised and the upper and lower parts of the vagina reanastomosed. If the septum is high, then a combined abdominal and vaginal approach is necessary. Occasionally, the septum is so large that either intestinal transposition or skin grafting is necessary to bridge the gap between the upper and lower vagina. Fertility is possible in these patients, as long as the cervix is normal, and has been reported in 40% to 50%.[30] Endometriosis may be a significant problem and should be reduced by prompt diagnosis and treatment.

LONG-TERM RESULTS OF GENITAL SURGERY

Genital surgery has several clearly defined aims. The external appearance must be cosmetically acceptable and clearly feminine. Penetrative intercourse must be possible and comfortable. Sensation should be preserved as much as possible to allow arousal and orgasm. In some cases, fertility is possible and should be preserved. Accurate and detailed long-term data are essential if we are to be able to counsel our patients appropriately about the choice of surgery. However, little information is available, partly because this is a difficult area to study. The physical consequences, such as stenosis due to scarring, may be difficult to separate from the psychological and psychosexual effects of requiring genital surgery in the first place. Other associated problems can have a major impact on sexual response, including XY karyotype and infertility. Although many papers are available in the literature, most give only immediate and short-term postsurgical results. Others that describe long-term follow-up do not detail how sexual satisfaction was addressed. The evaluation of "success rates" in vaginoplasty is difficult to standardize, and many papers do not specify their end points. Papers report "normal" intercourse or "normal" vaginal length without describing what they mean by "normal."

Long-Term Outlook after Vaginoplasty

If vaginal dilators fail or are not appropriate, the surgical techniques that are the least invasive are the Williams vulvovaginoplasty and the Vecchietti operation. There are no long-term data on the Williams procedure, and it is rarely performed nowadays. The vagina created by this method does not stenose, and long-term results may also be good, although evaluation is necessary. The vagina does run at a far more horizontal angle than normal, and some patients complain that a feeling of penetration is lacking. The Vecchietti operation is suitable only for women without previous vaginal surgery. Conditions such as AIS or Mayer-Rokitansky-Küster-Hauser syndrome are most appropriately treated with this procedure if previous vaginoplasty has not been attempted. The operation has been used in some centers in Europe for many years with good reported success rates and low morbidity but short follow-up.[31] If long-term results are also good, then its use is likely to become more widespread. In both the Williams and the Vecchietti procedures, the recovery period is short and complications are rare.

If the procedures previously described are not indicated, then the surgeon and patient need to consider more invasive and major operations. The McIndoe-Read vaginoplasty is probably the most widely used procedure. Surgery can be straightforward but also can be complex, particularly in the presence of scarring from earlier operations. Despite the frequency of its use, the long-term data are patchy, with reports of significant vaginal stenosis and contracture.[32] Few studies have reported detailed results on sexual function, although satisfactory intercourse is reported in up to 85% of women who have undergone this procedure.[33] Detailed assessment including vaginal examination would contribute to this debate. Few papers have commented on the unsightly scarring from a donor site, which can be a significant embarrassment for young women. The Davydov procedure avoids donor area scarring, and small series have produced good short- and medium-term results. Early studies have assessed sexual function, and the reports are encouraging.[34]

The most complex surgery is intestinal transposition, which involves major abdominal and vaginal surgery and is time-consuming and complex. The main advantage of this procedure is that contraction is not a problem. Reported success rates in small series have been high. Martinez-Mora and coworkers[35] reported complete success with "normal" intercourse and orgasm in 18 of 19 patients. However, persistent offensive vaginal discharge and bleeding can occur, and diversion colitis has been reported and can be very difficult to treat.[17]

Although long-term data would be helpful, some procedures are not suitable for certain groups of patients. There is no ideal operation suiting all women, and decisions must be tailored to the individual patient. At least, better awareness of risks and complications would allow the surgeon and patient to make a more informed decision.

Long-Term Outlook after Feminizing Genitoplasty for Congenital Adrenal Hyperplasia

Conventional treatment for CAH is to perform a feminizing genitoplasty early in childhood. This decision is made by the medical team, usually with the involvement of the parents. The only person not involved in the decision is the child. It has been accepted that, because these girls have a female karyotype and are potentially fertile, surgery should render the genitalia as female as possible to allow complete integration into the female gender role. However, with the increasing input from patient support groups, it is becoming clearer that the outcome of surgery is often unsatisfactory. The effects of surgery are irreversible, and the child is left to make the best of it as an adolescent and adult. Although there is not much long-term data, much of it confirms patient dissatisfaction with the results of the surgery. Studies are small, and the assessment of sexual function is often scanty. It can, of course, be difficult to draw firm conclusions, because the effects on sexuality must be multifactorial and include not only surgery but also hormonal effects, both prenatal and postnatal. There is good evidence now to suggest that the excess androgens produced in this condition have an effect on the fetal brain before birth, which may profoundly affect sexuality.

Nevertheless, it is essential that we try to collate as much long-term data as possible to allow the patient and the family to make the best possible decision. The phrase "long-term" is used often in papers but may refer to "surgical success" rather than later sexual function. Whereas this information is valuable to surgeons, it is often not very helpful to the child or the parents in making decisions about surgery. For example, Donahoe and Gustafson[36] presented long-term results of surgical treatment ranging from 26 to 32 months in children aged between 2 and 9 years. Other studies that did contain long-term adult follow-up gave scanty details as to how sexual satisfaction was assessed. Newman and associates[37] evaluated 79 girls over a 25-year follow-up period. Twenty of these had long-term follow-up. Twelve had had clitoral surgery only, 10 of whom showed "highly satisfactory" sexual function. Eight patients had had vaginal and clitoral surgery, and in this group sexual function was described as "satisfactory to poor." No details were given as to how this was assessed.

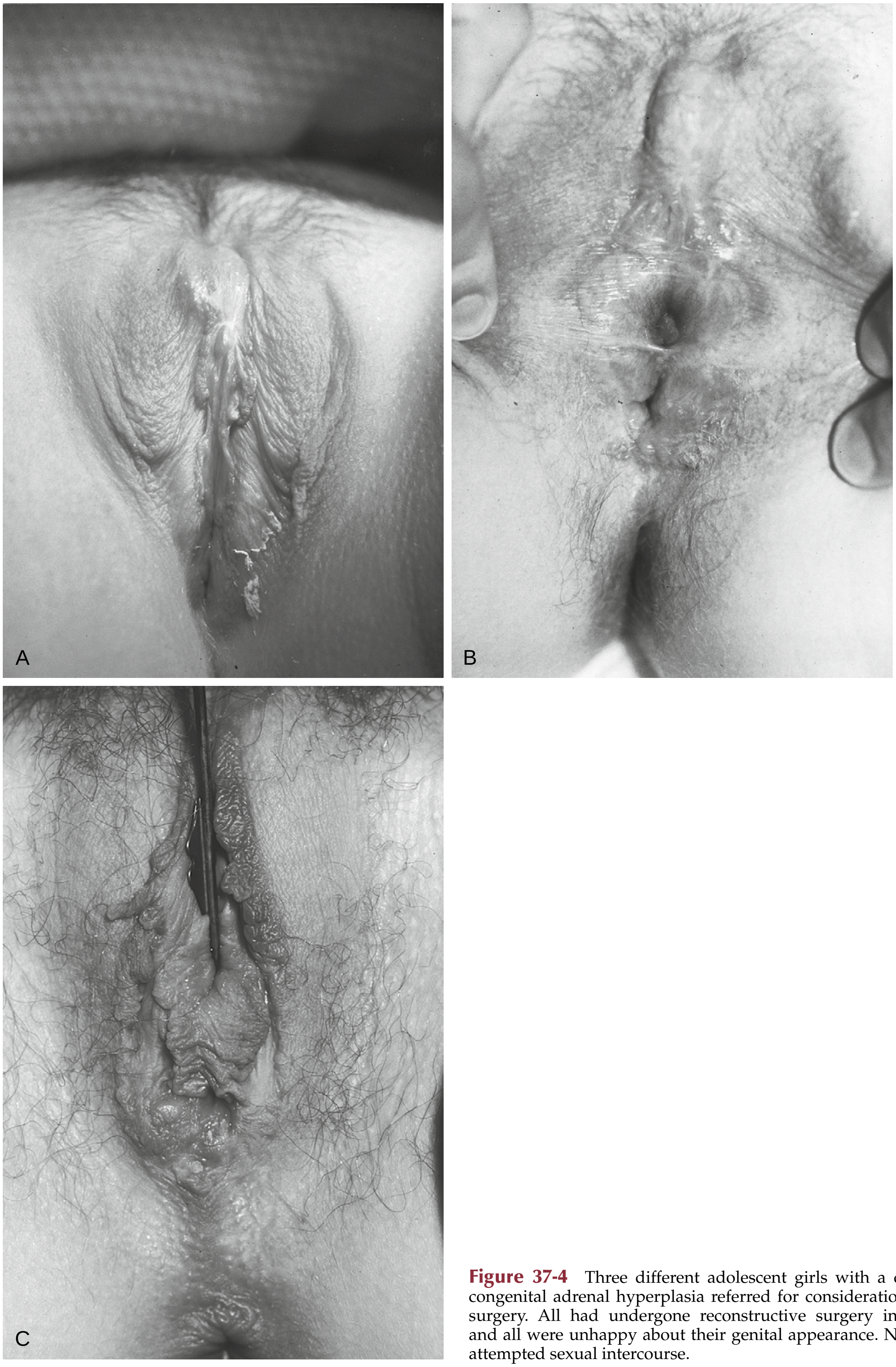

Figure 37-4 Three different adolescent girls with a diagnosis of congenital adrenal hyperplasia referred for consideration of further surgery. All had undergone reconstructive surgery in childhood, and all were unhappy about their genital appearance. None had yet attempted sexual intercourse.

The need for further modification of vaginal surgery is well recognized, but again there are few data. The clitoris may require further reduction during adolescence. The reason for this is unknown, although in some cases it may be due to poor compliance with steroid medication for the CAH. It is likely that each surgical attempt will further reduce sensation. The vagina may also need further enlargement to facilitate tampon use and, eventually, intercourse. In addition, the cosmetic appearance of the external genitalia may not be acceptable and can cause great distress to an adolescent girl (Fig. 37-4). Alizai and coworkers[38] reported on 13 adolescent girls (mean age, 13 years) who had undergone reconstructive surgery in childhood and found that all would need more surgery to allow intercourse as adults. Similar findings were reported by Creighton and associates in 2001.[39]

There is also limited information available on sexual function after feminizing surgery, but what data there are again suggest a detrimental impact of surgery. Dittmann and colleagues[40] evaluated 34 female patients with CAH and compared them with 14 non-CAH sisters. In their study, the women with CAH were less likely to have experienced sexual activity with male partners. However, May and associates[41] reported that more than half of their sample of women with CAH, most of whom had had genital surgery, had current pain with intercourse as well as considerable anxiety about sex. A cross-sectional study by Minto and colleagues[42] evaluated 39 women with ambiguous genitalia; 28 had been sexually active, and all had sexual difficulties. The 18 women who had undergone clitoral surgery had higher rates of nonsensuality (78%) and of inability to achieve orgasm (39%) than did the 10 who had not had surgery (20% and 0% respectively). These are certainly poor results and should lead us again to question the role of early genital surgery. Sensory testing of the genital area has also demonstrated a loss of sensation in women with a past history of clitoral surgery.[43]

Perhaps we should question whether surgery for moderate and mild virilization in childhood is harmful rather than beneficial. Some surgeons have suggested that a policy of "watchful waiting" may in some cases be preferable to early genital surgery.[44] This would allow the patient to have a role in the decision about surgery. Some women with clitoral hypertrophy may decide not to have surgery that could reduce sensitivity and impair sexual response. It is essential that parents making decisions have this information before consenting to clitoral surgery. The option of psychological support as a realistic alternative to surgery must be discussed.

CONCLUSION

It is becoming more clear to specialists in the field of reconstructive genital surgery that long-term success rates in relation to sexual function are highly variable. Whereas some patients seem to have good results, others obviously do not. The emergence of patient support groups has increased awareness of patient dissatisfaction. The range of types of surgery available is large, but success rates are unpredictable and complications are not uncommon. The decision to undergo surgery is a difficult one to make, although a decision not to do so may mean, in effect, a decision not to have a conventional sexual relationship. The only person who can make the final decision is the patient, with our support and advice. It is our role to provide as much information as possible to allow that decision to be a fully informed one. If surgery is the correct choice, then the timing of it also needs consideration. In some cases, such as feminizing genitoplasty for CAH, better results may be obtained by delayed surgery, because it would reduce the number of procedures required and allow the patient greater input into the decision. Whether or not this is true may be explained by better long-term follow-up data.

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CHAPTER 38

AMBIGUOUS GENITALIA IN MALE ADOLESCENTS

C.R.J. Woodhouse

The study of individuals born with ambiguous genitalia is undergoing a revolution. In the past, the birth of such a baby was regarded as a medical emergency. The management was based on defining the diagnosis as closely as possible, choosing the most "appropriate" gender, and sticking to it. Most children were never told of their original diagnosis, especially if the gender chosen was different from their genotype.

Anecdotally, in the Western world most babies were raised female because the genitalia were easier to reconstruct. In poorer regions, most seem to have been raised male because boys were considered more valuable than girls. This suggests that in neither culture were the baby's best medical interests the foremost consideration. It is not possible to divorce the care of a child from the environment in which it is to live, and such policies may be just as acceptable as more strictly scientific ones.

Little has been written on the late outcomes of such babies. That which has been written mainly concerns easily measurable features such as pregnancy rates. However, future patients should benefit greatly from a broader approach based on quality-of-life measurements. Although this goal is laudable, quality of life is difficult to define and measure, especially in adolescents. Instruments that are available have been validated mainly in adults. Those used for children and adolescents are most often for specific and fairly common conditions such as diabetes. Opinions are most often collected from parents and caregivers rather than from the child.[1]

A further problem is our limited knowledge of sexuality. Men and animals have been extensively studied. Scientific study of female sexuality is a comparatively new field, at least as far as the surgeon is concerned. Well-known researchers such as Kinsey or Masters and Johnson recorded female sexual behavior and normal sexual physiology. It was only in the 1990s that detailed work on female sexual dysfunction was published.[2] Some follow-up on vaginoplasty has been limited to assessments of patency, penetration, and fertility without considering the quality of the sexual experience. Papers refer to the vagina being "satisfactory" without saying to whom it was satisfactory or by what means satisfaction was measured.

Such limited assessment may not be totally invalid. The strictly surgical results could be thought of purely in terms of the ability to create a "vagina" where none previously existed, on the presumption that an infant was to be raised female. However, although it may be self-evident that a penis made from a forearm flap does not have physiologic sexual function, the medical establishment may be less aware that a vagina made from intestine is also sexually inert. The fact that a surgeon can make a "vagina" more easily than a "penis" should not, on its own, be a reason to make a female gender assignment.

It is becoming clear from animal work and from clinical observation that the brain is a dominant organ in sexual orientation.[3,4] It is, therefore, not surprising that babies exposed to androgens in utero should exhibit some behaviors more often associated with boys, regardless of the appearance of the genitalia.

The current revolution, led in part by adult patients themselves, questions previously held notions, requires a flexible approach to allow a gender change in later life, and draws attention to the larger number of affected adults than was previously known. Despite the difficulties in assessing quality of life and management success in a broader context than "surgical" outcome, changes in the management are demanded. It remains to be seen whether the changes will be for the better.

THE PENIS

Micropenis

In disorders of sex development (DSD), those with an inadequate penis are usually undervirilized males, most of whom have an XY karyotype. The policy for many years has been to advise a male sex assignment, especially if the hormonal environment in utero has been androgenic. Occasionally, infants who have a 46,XX karyotype but are heavily virilized are raised as males, but almost by definition they will have an "adequate" penis (Fig. 38-1).

A micropenis is defined as one with a stretched length that is more than 2 standard deviations (SD) below the norm. Some are responsive to androgens and, particularly with intermittent doses of testosterone, may grow into the 10th to 25th percentile range. For many, however, growth is limited to that which would be expected of non–androgen-sensitive organs (Fig. 38-2).

Absent or Very Inadequate Penis

The very rare condition of aphallia is barely worth mentioning, not because of a lack importance but because there are no useful data. Skoog and Belman reviewed the world literature up to 1989. Of the 50 patients identified, 15 had died in childhood from associated congenital anomalies.[5] Female sex assignment was recommended, but this seems to have been on the basis that construction of female genitalia was easier than that for males. This view was supported by Hendren in a report of five patients, all of whom were raised as females.[6] However, there are no reports of the outcome in adult life of such a policy. In a survey of pediatric urology units in the United Kingdom and Eire, no adult cases were identified. There are occasional case reports of individuals raised as males, including one who first presented at 16 years of age.[7]

A consensus meeting on DSD in 2005 recommended a male assignment, primarily on the basis that normal androgenization of a 46,XY fetus leads to a strong male identity in more than half of patients raised as females and in most of those raised as males. Only 2 of the 84 patients in the relevant study had aphallia.[8]

If the baby is to be raised male, a temporary phallus may be made with a skin flap in childhood, providing it does not compromise a subsequent formal phalloplasty in adulthood.

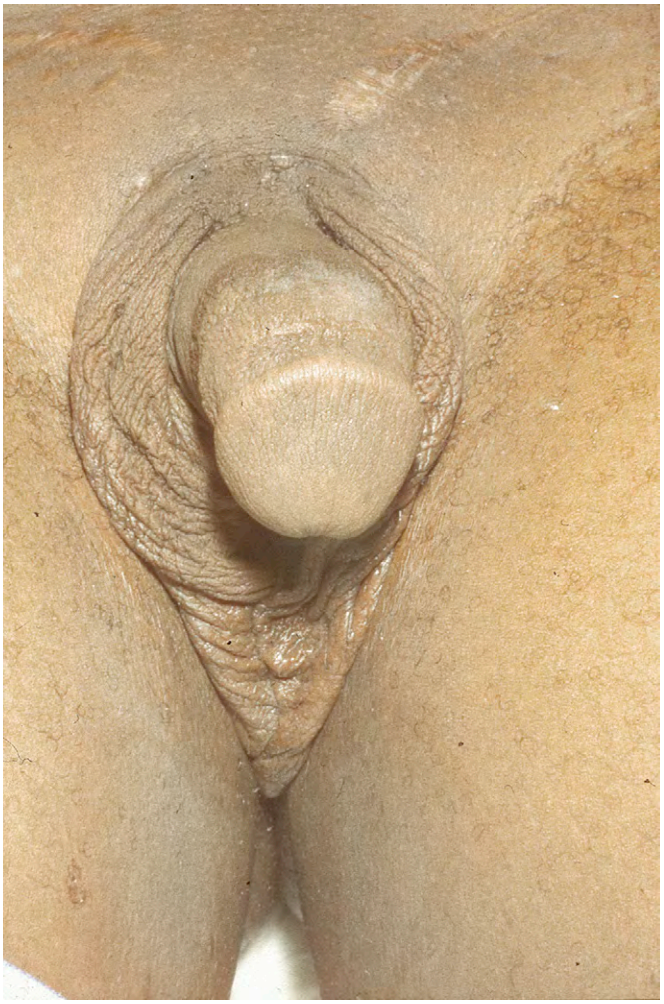

Figure 38-1 Clinical photograph of the penis of an adult 46,XX patient raised as a male.

In the rare conditions of complete androgen insensitivity (CAIS) and cloacal exstrophy, female reassignment has been usual. The pediatric literature supports this view, and follow-up before puberty suggests that this policy can be successful and that those raised as males have severe psychological problems. In patients with CAIS raised as females, the outcomes in adult life have been very satisfactory.[9]

Cloacal exstrophy, although rare, represents the extreme example of the dilemma. There is a wide range of defects affecting the spinal cord, the intestine, the genitourinary tract, and the abdominal wall. The options for reconstruction are limited, and it is a surgical triumph for these babies just to survive. However, in males the chromosomes are normal 46,XY. The penis is rudimentary or even absent, but the testes are normal.[10] Most surviving males have been reassigned to female gender, but few have yet reached adult maturity. In the largest personal series, this policy appears to have been successful. In all of 14 patients born with 46,XY chromosomes, the children had typical feminine core gender identity but also demonstrated some male role behavior.[11]

The broader literature gives contradictory results, albeit with only case reports and small series. In a very detailed review by Meyer-Bahlburg, 50 patients with cloacal exstrophy who were 46,XY and were assigned to the female gender at birth were identified from 1973 to 2005. The age at follow-up ranged from 5 to more than 30 years. Eleven patients had reverted to the male gender, and 7 of those living as females had gender dysphoria. Therefore, female gender was successfully maintained in only 64%, and only 8 patients had reached adulthood.[12]

There is no “right answer” for sex assignment in many DSD conditions, but it is reasonable to question previously held beliefs in light of the limited adult data available. A decision to raise a child as female should not be based exclusively on the notion that it is easier for the surgeon to create “female genitalia” than “male genitalia,” especially if the infant has the potential for fertility as a male.

SURGICAL ENLARGEMENT

There is no operation in childhood to make a small penis larger. The popular press sometimes carries sensational stories of techniques for penile enlargement. These, and magazine photographs, may raise expectations that cannot be achieved with our present state of knowledge. The medical literature has very little to say on the subject. Normal values for penile size and criteria for enlargement have been established (Fig. 38-3).[13,14] Men with DSD usually (but not always) have a penis well below these normal values. Not surprisingly, most are, to varying degrees, worried about their apparent inadequacy. Although they may have reasonable cause for worry, it should not be forgotten that genital size is a common adolescent concern.[15]

All authors recommend psychiatric assessment before surgery for penile enlargement is considered. I have found this to be of limited value in men with such small penises. Except for those with overt psychiatric disease, there is little that can be said except that the penis is, indeed, very small. Sympathetic counseling by someone with a special knowledge of DSD conditions is often helpful.

The overwhelming difficulty in enlarging a penis by surgery is that corporeal tissue cannot be made. The basis of surgery is, therefore, to make the best use of the available material. It is possible to reduce the size of the suprapubic fat pad and to unbury a buried penis. Apart from this, the techniques used for enlarging the more normal penis might be applied, but there are no series reporting their application to patients with DSD in the literature.

Length may be increased by division of the suspensory ligament and subsequent application of weights to the penis. The results of this procedure are controversial, and the lengthening, such as it is, appears only in the flaccid state.[16] The erect penis is no longer than before and may be unstable, having lost part of its attachment to the pubis.[17]

The most widely reported method of increasing girth is by the injection of autologous fat. However, the results are very poor because of the irregular necrosis and reabsorption of the fat.[17] This procedure has not been reported for micropenis, and it seems likely that the results would be just as bad. The girth of the tunica albuginea of the penis can be increased by longitudinal incision and patching with opened saphenous vein. In the single published series, several of the organs were described as hypoplastic with a girth 2 SDs below the mean, which is similar to that seen in DSD conditions. There was minimal change in flaccid diameter but a mean increase of about 1.5 cm in the diameter of the erect penis in the hypoplastic cases.[18] The increase in erect diameter would be particularly useful in cases of DSD.

If no penis is present, or if a major addition is to be made to a very small penis, the impossibility of creating cavernous tissue is even more significant. The new phallus does not have natural erectile function. A very good penis can be made for patients undergoing female-to-male reassignment for gender

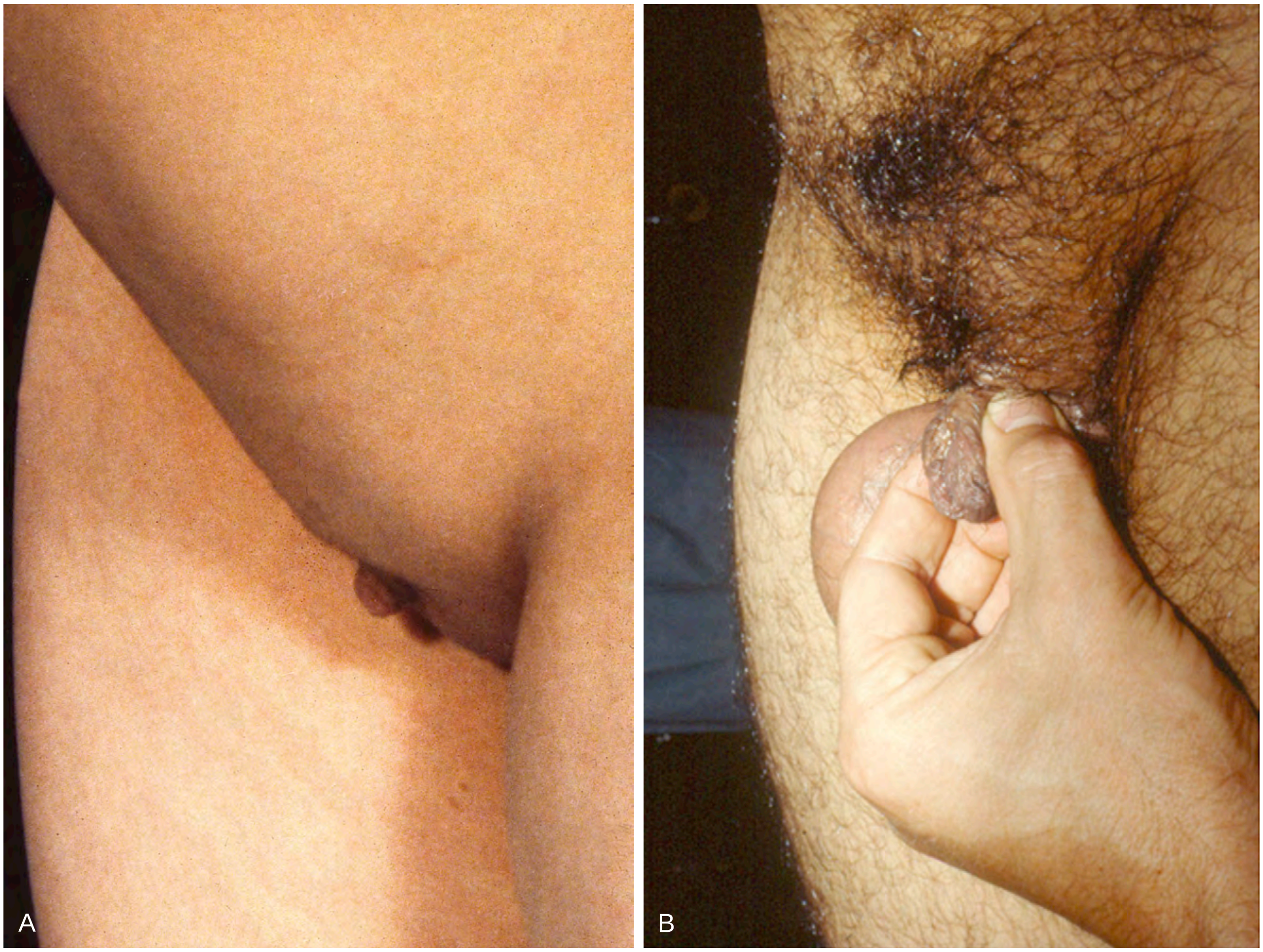

Figure 38-2 Clinical photographs of patients with micropenis in childhood **(A)** and after puberty **(B).**

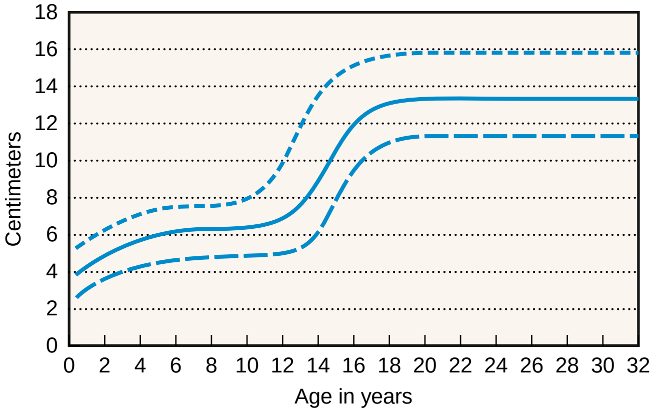

Figure 38-3 Growth of penis in length from birth to maturity. The solid line indicates the 50th percentile, and the dotted lines describe the 90th and 10th percentiles for the stretched penis. (From Schonfeld WA. Primary and secondary sexual characteristics. *Am J Dis Child.* 1943;65:535-549.)

dysphoria. Similar techniques could be used for patients with DSD, but experience is limited to occasional cases. If the procedure is done in childhood, the phallus does not grow at puberty.

If the penis is completely absent, a new penis can be formed from skin flaps using the techniques developed for gender reassignment. Good technical results have been reported in boys with micropenis using either groin flaps or microsurgical transfer of a forearm flap.[19,20] The microsurgical technique is claimed to allow return of tactile sensation and even, with time, erogenous sensation. No attempt was made to insert prostheses for erection, and there is no report on the sexual results, if any.

A technique has been described to make a phallus from a skin flap, using the technique for female-to-male gender reassignment, and to “piggy-back” it onto the natural penis. The man then has his own sexual satisfaction from his small natural penis and can penetrate his partner’s vagina with the reconstructed part. The results in patients are reported to be good with very careful selection.[21,22] In my own very limited experience of the procedure, the appearance is odd, and I am doubtful whether it can be justified except in those with a very rudimentary natural penis (Fig. 38-4).

It is most important that parents and children be given a realistic view of the very limited achievements of surgery. Widespread use of the Internet may give the impression that penile enlargement, tissue engineering, and even penile transplants are immediately available. Autologous cavernosal tissue has been grown in the laboratory and used to form a functioning penis in rabbits. This may be the way of the future, but it is not a clinical reality at present.[23]

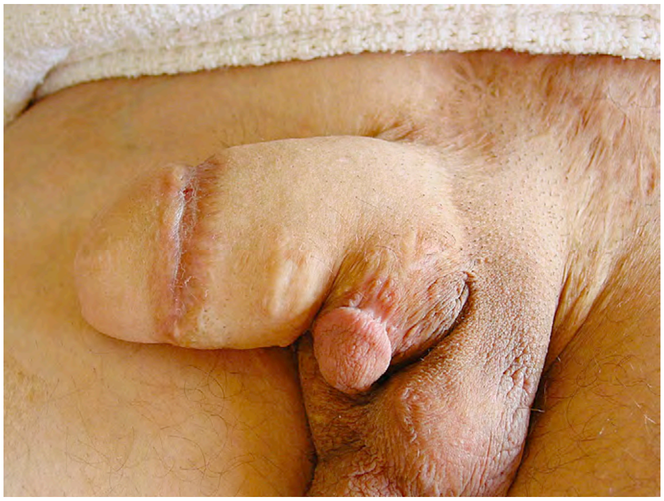

Figure 38-4 Clinical photograph of a phallus constructed from a forearm skin flap *(above)* "piggy-backed" onto a micropenis. (Courtesy of D.R. Ralph.)

Medical Enlargement

The early management of any case of ambiguous genitalia is that of the underlying condition. With endocrine correction, there may be some growth of the penis. Further growth is possible when puberty is induced. Dihydrotestosterone cream has been used to stimulate penile growth. Both the penis and the prostate show rapid growth. In a series of 22 children, there was a mean increase in length of 53% in the first month and a further 18% in the second month of treatment. The series included 4 boys who had failed to respond to testosterone treatment.[24] Late treatment of a 12-year-old and a 17-year-old boy has been reported, but the responses were poor.[25] The cream is not freely available.

FUNCTION OF THE SMALL PENIS

Among those patients with most severe hypospadias, there is a considerable overlap with DSD, especially androgen insensitivity syndromes. In one series of posterior hypospadias, 13 of 42 men had a major DSD anomaly. All had severe hypospadias (usually perineoscrotal) and micropenis.[26] Even with hypospadias as severe as this, intercourse still occurs. In a series of 19 patients born with ambiguous genitalia subsequently determined to be caused only by perineal hypospadias, it was reported that 63% had had intercourse. However, only 4 had a regular partner. None of the 13 patients had sperm in their ejaculate.[27] Less good figures were given in the series of Eberle and colleagues: Although 25 of 42 patients reported satisfactory erections, masturbation, and ejaculation, few had had sexual intercourse. Nine of 42 were married and 3 had children, but only 6 had a stable relationship.[26]

Men with a very small penis can have satisfying sexual intercourse with female partners. In a series of 20 men from my own unit with a variety of diagnoses, all were heterosexual in orientation, 75% had a regular partner, and none wished to have a gender reassignment.[28] Very similar figures were reported in an abstract. All of 20 patients had a strong male identity, and 15 had had intercourse. Sixty-four percent of those who had had intercourse had misgivings about their penile length before their first intercourse, but only 41% did so afterward (T. Mazur et al., personal communication, 2000).

It seems, therefore, that an abnormal or rudimentary phallus can form the basis for sexual activity in a male role. Nothing is known of the satisfaction of the sexual partners, but it would be unreasonable to base decisions as to the gender of rearing of a baby on the opinions of a putative partner some years in the future.

FERTILITY

With the advent of reproductive technologies, it has become much easier to treat male factor infertility. When fertility depended on the ejaculation of adequate numbers of viable sperm, there was little that could be done to help the infertile male. Now, providing the testis makes some sperm (and, in future, perhaps sperm precursors), several options are available. In making a sex assignment, the prospect for fertility in the assigned sex becomes very important. Although the documented cases of male fertility have been primarily in the relatively "fringe" conditions of DSD, they do illustrate that even the most unpromising testes can produce genetic material.[29] The presence of a Y chromosome, or even a fragment thereof, should be influential in assigning a male sex of rearing.

Klinefelter's Syndrome

Karyotype abnormalities are eight times more common in men with nonobstructive azoospermia than in the normal population. Of these men, 83% have Klinefelter's syndrome.[30]

Klinefelter's syndrome is surprisingly common, occurring in 1 of every 500 male live births. It is seldom diagnosed until adolescence, because the genitalia are normal. At puberty, some secondary sexual characteristics develop, but the testes remain small and soft. Characteristically, the boys grow tall (with particularly long legs), have gynecomastia, and appear eunuchoid. The karyotype is 47,XXY in 85% of cases and mosaic (46,XY/47,XXY) in the remainder. In the past, all patients with the complete form were thought to be azoospermic, and testicular biopsies showed the presence of hyalinized seminiferous tubules and Leydig cell hyperplasia; mosaics were known to have some spermatogenesis. It is now clear, however, that there is a spectrum of germ cell function (Table 38-1).[31]

Until recently, patients with Klinefelter's syndrome were considered to be infertile. There have been successful pregnancies using testicular sperm for intracytoplasmic sperm injection (ICSI). Preimplantation genetic analysis of embryos has not shown a recurrence of Klinefelter's syndrome, the karyotypes being 46,XX or 46,XY.[31-33]

5α-Reductase Deficiency

Three men born with 5α-reductase deficiency have been reported to have fathered children. In one case, two boys and one girl were produced in two pregnancies by intrauterine insemination. The other two men fathered one child each by intercourse.[34,35]

Hypogonadal Hypogonadism

Hypogonadal hypogonadism is rare and produces a wide spectrum of phenotype. Kallmann's syndrome is but one group. Some have severe micropenis. In adults, it is useful to divide these men into those with testicular volumes greater than or less than 4 mL. Long-term treatment with human chorionic gonadotropin (hCG) raises the serum testosterone, but not into the normal range. The larger testes respond better.

Table 38-1 **Findings of Sperm in 52 Men with Non-mosaic 47,XXY Klinefelter's Syndrome**

	Ejaculate	Testis
Sperm	4	1
ICSI	3	1
Pregnancy	2	1
Normal baby	0	1

Data from Kitamura M, Matsumiya K, Koga M, et al. Ejaculated spermatozoa in men with non-mosaic Klinefelter's syndrome. *Int J Urol.* 2000;7:88-92.

ICSI, intracytoplasmic sperm injection.

Erectile and ejaculatory function are almost always improved. Spermatogenesis is then found in about one third of those with the smaller testes and in 71% of those with larger testes.[36] Fertility in Kallmann's syndrome, with or without hormone supplements, has been recognized for many years.[37]

GONADAL NEOPLASIA

Both "male" and "female" gonads are at risk of neoplasia. If there were no prospect of fertility, it would be reasonably easy to suggest removal of all gonads even when the risk is small. Now, a more accurate assessment of risk is essential.

The greatest risk is in those with a Y chromosome (although without a Y chromosome male fertility is improbable). It also seems likely that the common precursor of neoplasms is carcinoma in situ arising from primordial germ cells (intratubular germ cell neoplasia, or IGCN). Although follow-up is incomplete, it is already known that 50% of men with IGCN will develop a germ cell tumor within 5 years, but it is probable that all would in time.[38] About 25% of DSD patients with a Y chromosome, especially if it is structurally abnormal, have IGCN on biopsy.

Several types of disorders of sex development carry an increased risk of testicular neoplasia, and management is frequently dictated by this possibility. The majority are germ cell neoplasms, so some germ cells must be present in the gonad, even if primitive and small in number. The more dysplastic the germ cells, the higher the risk of neoplasia.

The highest risk is in patients with mixed gonadal dysgenesis who may have a 46,XY or a mosaic 46,XY/45,XO karyotype. Ninety percent have undescended gonads which either are streaks or contain some testicular tissue and may be different on the two side. Gonadoblastoma is rare in patients with 46,XX karyotype and dysgenetic gonads; this is not surprising, because the gonadoblastoma locus is on the Y chromosome.[39]

The usual tumor is a gonadoblastoma. This is a mixed tumor of Sertoli cells and germ cells, with occasional Leydig cells. The gonadoblastoma never metastasizes and may even regress, but in one third of cases the germ cell portion becomes malignant. The endocrine cells may secrete active hormones, especially testosterone.[40] The tumors may occur, albeit rarely, in utero or in childhood.[41] The incidence rises rapidly after puberty and is highest at the usual age for germ cell tumors, in the second and third decades. They are bilateral in about one third of cases.

In series of 102 DSD patients at the Hospital for Children, Great Ormond Street, 38 children had gonadal dysgenesis, 3 of whom developed neoplasia at a median age of 2.5 years.[42] But in a series of older DSD patients reported by Savage and Lowe, four of five cases of neoplasia occurred in the second decade.[40]

In androgen insensitivity, especially in its complete form (CAIS), seminomas occur. They are rare in childhood but more common in the second and third decades. Three cases have been reported in siblings.[43] Individuals with CAIS and those with the partial condition who are raised as females should have their gonads removed in infancy. Some gonads may produce enough estrogen to induce a female puberty, so parents may wish for the gonads to be preserved, recognizing that the earliest recorded neoplasms have occurred at 14 years of age.

True hermaphrodites must, by definition, have both ovarian and testicular tissue. Most have the 46,XX karyotype, and one third are mosaics. Testicular tissue develops in spite of the absence of a Y chromosome, although usually in the form of an ovotestis. Those with a Y chromosome have a higher chance of having an identifiable testis and are at particular risk of developing a germ cell neoplasm.

The condition accounts for only 10% of DSD patients. A wide variety of tumors have been described, often as case reports. Gonadoblastoma and seminoma/dysgerminoma are the most common types. Teratoma, Brenner tumor and mucinous cystadenoma have also been reported.[40] In the ovarian gonads, a juvenile form of granulosa cell tumor occurs, 10% of which are malignant. They arise from ovarian mesenchyme and are estrogen secreting. Characteristically, they recur many years after the initial removal.[44]

On testicular biopsy, abnormal cells can be seen that precede the development of carcinoma in situ. The finding of these cells in a patient with male phenotype and 45,XO/46,XY karyotype indicates a high risk of neoplasia and is an indication for gonadectomy.[45] However, recent work has suggested that a biopsy should be done at about the time of puberty in all who are at risk. If IGCN is not present, the gonads may be retained and a policy of watchful expectancy followed. Those individuals who do have IGCN should bank semen (if spermatogenesis is present) and receive radiotherapy.[38]

REFERENCES

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CHAPTER 39

PSYCHOLOGICAL AND PSYCHIATRIC ASPECTS OF GENITOURINARY CONDITIONS

William G. Reiner

THE DEVELOPMENTAL TASKS OF CHILDHOOD

Human development is a lifelong set of processes from the zygote through embryo and fetus, infant and child, adolescent and adult. Growth and maturation are its rubrics; childhood emphasizes its unfolding. Genitourinary conditions in children emerge within the dynamic context of this global development. Most pediatric genitourinary conditions affect child development, are affected by it, or both. The child's reactions reflexively relate the level of the child's development and developmental potential as influenced by medical realities and surgical interventions. Children vary in their vulnerability to urologic anomalies, just as they do to other, concurrent or unrelated developmental aberrations. Understanding some of the more important forms and functions of child development and their dysfunctions relative to genitourinary conditions will assist the pediatric urologist in communicating with both child and parents, educating the parents for informed consent and compliance, accentuating the child's ability to cope and comply, and providing good medical care.

The behavioral fields have fairly delineated some of the expectations of normal, or typical, children in terms of gross psychosocial, emotional, and cognitive development. However, illness, and especially chronic illness, affects development with incompletely appreciated consequences emanating from poorly deciphered mechanisms. Vulnerabilities as well as resilience may seem almost mysterious. Therefore, to comprehend the developmental tasks specific to children with genitourinary conditions, it would be best to contrast their psychological outcomes with the developmental profiles of normal children. This is a forbidding task, because few longitudinal studies of development exist for even the normal situation. Some profiles, such as psychosexual development in normal children, have been poorly studied, if at all.[1] Nevertheless, important observations about child development, especially in terms of genitourinary anomalies, can greatly benefit the urologist's goals.

Childhood can be divided somewhat arbitrarily into developmental categories or stages. For pediatric urology, useful divisions might include the periods of prenatal life, infancy, toddlerhood, from about 4 to 7 years, 8 to 10 years, and 11 years or older. Although such categorization is useful, it cannot belie the importance of the continuity of development from conception through birth and all postnatal life. Temperament and core personality traits, for example, are amazingly persistent throughout childhood, leading to a remarkable interactional consistency between temperament and environmental influences and realities.[2] In other words, the child not only responds to the environment but initiates his own environmental influences, thereby contributing to his own life experience. The child does not simply react but also interacts. Similarly, progressive sensorimotor development is a hallmark of childhood. Yet motor and correlated sensory functions do not necessarily develop simultaneously or even at similar rates. It is important, therefore, to work with the child and with the parents based on the child's developmental contingencies as well as the child-parent relationship.

For example, there is a sensorimotor developmental period during which important foundations of language are laid. The development of autonomous motor and sensory functions, including early social and communication skills, highlights the toddler period. The preschool years see progressive development of motor and cognitive skills, including language development, in early planning and organizing abilities. Although their ability to generalize is underdeveloped, children in this period internalize a goal orientation and a sense of self-worth when accomplishing goals. They do not abstract, nor do they operationalize from an internal sense of rules or structure. They have a poorly developed sense of cause and effect that affects their understanding of illness, mostly in terms of magical thinking. Figure 39-1 depicts typical language development as it relates to a child's developmental stage or level. When we recognize that language motor-development as well as expressive language skills precede receptive language development, we can better predict how a child with a given temperament might respond to a given situation and explanation. In other words, children can speak much more coherently than they comprehend at any given age.

The failure to recognize how little a child comprehends compared to how well she speaks, especially before about 11 years of age, leads to all sorts of frustrations between the child and her doctor as well as her parents. Moreover, it is not until about 8 years of age that children begin to recognize that they are not comprehending—although they are unlikely to volunteer such recognition. There is a similar lag between many other motor functions and their neurologically correlated sensory comprehensions. For example, very young children can often learn to void, or to withhold urine or stool, before they fully comprehend the sensory input from the bladder or rectum. Such normal neurologic developmental lags, together with inappropriately timed environmental instructions or demands, probably play a role in the etiology of conditions such as the voiding dysfunction syndrome. Even if it is inadvertent, active maladaptive input from the child or the parents more than likely influences the complex continued development of the system: bladder-midpons-frontal lobe connectivity and function may maladapt.

The school-age child is preparing for puberty and adolescence. His growing autonomy contrasts with an accentuated need for conformity with peer activities and attitudes. Success and recognition are very important in terms of social, academic, and athletic competence. School and home are the primary seats of his life. In the school-age child, cause-and-effect implications gradually become an important rubric for understanding illness, trauma, and surgery. The magical beliefs regarding illness and treatment begin to wane as the transformations of prepubescence and of puberty lead the child into a more cognitively oriented adolescence. Psychosocial and psychosexual developmental phenomena become critical components necessary to successful maneuvering through childhood and adolescence into adulthood. Cognitive functions become

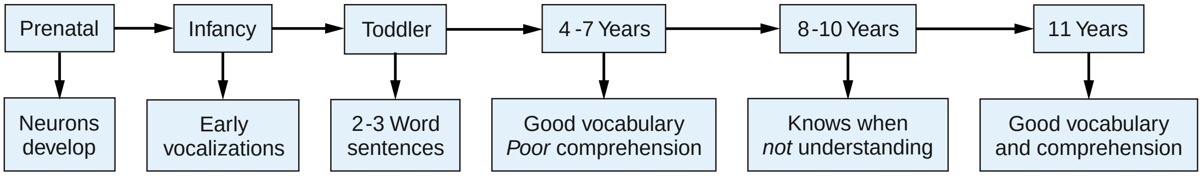

Figure 39-1 Expressive and receptive language development by age.

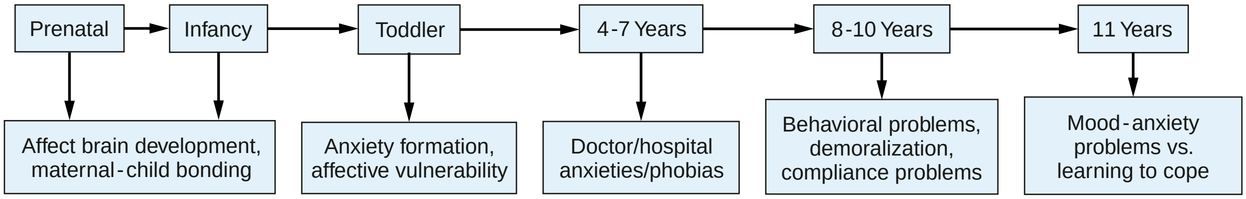
Prenatal
Infancy
Toddler
4-7 Years
8-10 Years
11 Years
Affect brain development, maternal-child bonding
Anxiety formation, affective vulnerability
Doctor/hospital anxieties/phobias
Behavioral problems, demoralization, compliance problems
Mood-anxiety problems vs. learning to cope

Figure 39-2 Potential effects of chronic illness and medical interventions on development, by age at insult.

increasingly complex as the adolescent learns to decipher, abstract, make judgments, relate to people, and manipulate the environment. At the same time, social, emotional, academic, and parental pressures accelerate and peak. The aging child faces striking contradictions between autonomy and dependence, the desire to function as an adult and the fear of growing up, the drive for interpersonal and sexual relationships and the fear of intimacy.

For these reasons, children display an amazing array of developing language abilities, cognitive potential, personality traits and temperament, social skills, and psychiatric vulnerabilities. The agreeable, older child is likely to be easy to approach, examine, or treat, whereas the very shy child or the cognitively rigid child can be challenging at all ages. The difficult child may surface in medical situations at a remarkably young age, even in late infancy or young toddler years.[3] The treating pediatric urologist must position a given child's unique and specific characteristics within the larger clinical context. This chapter deals with some of the more important developmental and psychological issues that affect this clinical context.

CHRONIC ILLNESS AND EARLY HOSPITALIZATION

Childhood illnesses coincide with major brain developments. Developmental milestones, language acquisition, cognitive skills, and behavior can all be affected. A number of studies have assessed general aspects of chronic illness and early hospitalization in children. The developmental stage of the child at the age of onset of a given condition influences her perception of the illness, her development, and the outcome.[4] Absence from normal social situations, such as school, influences development. The precise relationships among hospitalization, pain and anxiety, malaise, and general brain development are unclear. Yet growth and development, the sense of self, body image, and social and sexual interests and behaviors interact with significant illness and surgeries in a complicated admixture of interconnected responses and learning. Additionally, chronic illness affects the family, including the siblings. Family functioning and the entire social network also play roles, even if these are difficult to measure.

Perrin and Gerrity, in a 1984 study, found that the nature and severity of an illness carry some developmental prognostic significance.[5] A serious illness in infancy may imply erratic bonding, difficulty in developing trust, and inhibited sensorimotor exploration. The unpredictability of the hospital environment may inhibit early autonomy or damage the sense of parental competency.[5] The physical constraints of surgery or hospitalization may inhibit the sense of self-control or the sense of being able to control the environment. Thus, toddlers or preschoolers may learn that the world of illness controls them, diluting their ability to attain a sense of initiative or to develop a sense of autonomy. Their early, innate difficulties with receptive language (comprehension) frequently lead to behaviors that health care providers and other adults are likely to misinterpret and to perceive as oppositional or immature rather than based on the anxieties associated with not understanding.

School-age children who have endured prior hospitalizations and surgeries are very likely to respond to new or recurrent situations much as they responded during their previous experience. An 8-year-old in preparation for a procedure may react much as he responded during a prior hospitalization at age 4 or 5 years, rather than as a typical 8-year-old. A young child may begin to envisage child-doctor communication problems as signs that doctors do not listen to him and that his perceptions are not important.

Early adolescents begin to weave their anomaly or chronic illness into their developing perception of self, including body image, identity, self-esteem, sexual self-esteem, and mastery or autonomy. Late adolescents perceive their condition within their growing sense of independence, their ability to abstract, their relations to others, and especially their understanding of their own sexuality and their sex of orientation. As Perrin and Gerrity noted, "Physical illness adds one more crisis to the already heavy dose of confusion adolescents have to cope with."[5] At the same time, such children may have a remarkably sophisticated understanding of their own illness or anomaly.[4] Such a child may display behavioral reactivity, demoralization, affective instability, maladaptive coping strategies, or abnormal illness behaviors.

Figure 39-2 depicts vulnerabilities by age of the child to chronic illness or medical interventions. Surgery or anesthesia may affect or disrupt hypothalamic-pituitary-adrenal (HPA) or hypothalamic-pituitary-gonadal (HPG) development or functions, with possible subsequent vulnerabilities to anxiety or affective disorders.[6]

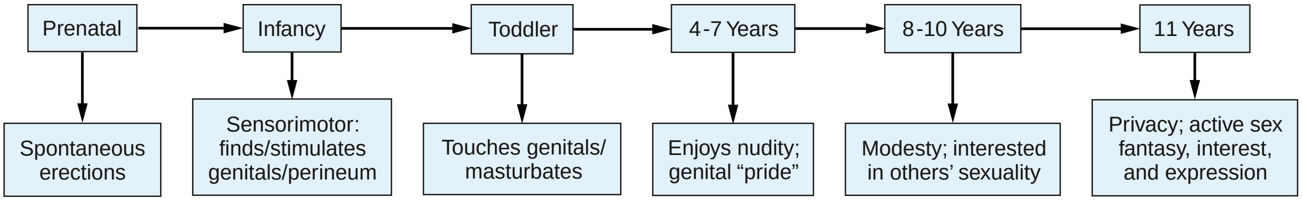
Prenatal
Infancy
Toddler
4-7 Years
8-10 Years
11 Years
Spontaneous erections
Sensorimotor: finds/stimulates genitals/perineum
Touches genitals/ masturbates
Enjoys nudity; genital "pride"
Modesty; interested in others' sexuality
Privacy; active sex fantasy, interest, and expression

Figure 39-3 Psychosexual developmental milestones.

UNIQUENESS OF GENITOURINARY PROBLEMS FOR DEVELOPMENT

Few studies have focused specifically on pediatric genitourinary conditions despite their relative frequency. Although brief medical experiences or single minor surgeries may have small effects on the development of most children, congenital anomalies, major reconstructions, and the peculiarity of urinary and especially genital reconstructions have potentially powerful developmental influences. The uniqueness of genitourinary problems in a developing child is underscored by potential psychosexual implications of both urinary and genital problems and by a resulting sense of being different. Pediatric urologists deal with childhood psychosexual development fairly routinely. However, the single chapter about childhood psychosexual development in each of the three major English-speaking textbooks of child and adolescent psychiatry offer discussions only of gender identity disorder, a rare condition. It should not be surprising, therefore, that so few actual data are available about normal psychosexual development in children.[1]

The observations about psychosexual developmental milestones that we do have, as depicted in Figure 39-3, are quite useful, if fairly basic. Some pediatric genitourinary conditions appear to be associated with inhibited psychosexual behaviors, especially those involving genital and perineal areas.[7] However, there is surprisingly little cross-sectional or longitudinal information on the developmental significance of early genital surgery or the psychological ramifications of early urologic disease.[7,8] The paucity of outcome data is rendered more problematic by the methodologic difficulties of the few extant (adult) studies.[9,10]

PROBLEMS PECULIAR TO URINARY CONDITIONS

Important to urologists, young children tend to confuse urinary and sexual functions. This is anatomically understandable. For children with genitourinary conditions, such confusion may be compounded by procedures on the urinary system that secondarily involve the genitalia, and vice versa. Incontinence becomes an additional confounding factor in psychosexual development. Experience has shown that perineal wetness may inhibit genital exploration, touching, grasping, and, secondarily, masturbation.[7] Because of the inhibition of such initial and early genital connectedness, one must surmise that early psychosexual development may be affected. Certainly, significant psychosexual developmental deficits are evident in adolescents with major genital anomalies.[7]

If strictly urinary conditions accentuate psychosexual and psychosocial developmental vulnerabilities, broader urologic conditions (e.g., myelomeningocele, bladder exstrophy) create more global developmental vulnerabilities. The genitourinary implications of such conditions appear to have a profound impact on the child's global developmental journey. For example, children with myelomeningocele or exstrophy encounter significant psychological repercussions of incontinence, sensorimotor dysfunction, and later issues of sexual function, fertility, and the implications of these for sexual relationships.[11] Adult studies imply that female patients may sometimes adapt better than males,[12] perhaps because genital issues are less problematic.

PROBLEMS PECULIAR TO GENITAL CONDITIONS

If urinary dysfunction affects psychosexual development, genital anomalies may present even larger psychosexual developmental uncertainties. Clinical outcome studies are few, but certain important developmental observations stand out. For example, anatomic deficiencies and surgical interventions can be constant reminders of inadequate genitalia. This may seem obvious for affected males, yet surgical interventions for female genital anomalies may impose a significant psychosexual developmental impact on these patients as well. Reconstructive genital surgeries can have broad potential psychosexual implications if performed in later childhood or adolescence, precisely because of an older child's increased awareness. Nevertheless, the psychological impact of genital reconstruction at any age is not entirely clear.

Sex chromosomal and other genetic abnormalities often carry specific implications for genital development. Poorly understood but important, these abnormalities may have broader developmental ramifications as well.[13] Children with disorders of sex development (DSD), for example, may have primary or secondary hypoactive sexual desire resulting from hypogonadism or from fear of sexual dysfunction, respectively.[14] They may have significant anxiety about a perceived lack of masculinity or femininity. They may experience impotence, premature ejaculation, anorgasmia, or genital sensory deficits. These conditions may escape detection without a specific, directed sexual history.

Such children require a comprehensive developmental approach. Strictly speaking, sexual development is one obvious area of concern. Yet even this implies vulnerabilities in terms of sexual function, sexual relations, and anxieties about sexuality in general. For example, impotence and premature ejaculation are almost always neurologic or anatomic in etiology. Anorgasmia is most commonly secondary to psychiatric medications, usually selective serotonin reuptake inhibitors (SSRIs) or neuroleptic medications. Genital sensory deficits can be secondary to neurologic disease or to surgical complications. Regardless of the cause, such conditions may imperil sexual self-esteem, sexual function, or sexual relationships for many years.

GENDER IDENTITY AND GENDER ROLE

Discussions about psychosexual development in children must include the nature of gender identity and gender role.[15] Identity itself appears to be an idiosyncratic and unique admixture of biology and its implications within human consciousness. It is innate and intuitive, yet almost impossible to define, especially individually. Gender identity is a reductionist sense of identity—that part of identity in which a person perceives and recognizes a personal sense of internal maleness or femaleness. The etiology of gender identity, the sexual dimorphism of gender, is only partly understood, even though sexual dimorphism is the most studied and best understood of all major embryologic processes. The intricacies of embryologic development include the complexities of the placenta, homeobox genes, genetic on–off switches, other epigenetic processes, nucleosomes, transporter proteins, receptor molecules, a plethora of ribonucleic acid activities, maternal and paternal gene imprinting, substantial variability in X chromosome inactivation in genetic females, and many other processes. The implications of such complexity for gender identity and gender role are largely beyond the scale of this chapter—and often beyond the reach of our present knowledge. Yet these implications are important to clinicians because of the clinical dilemma posed by the newborn with significantly anomalous genitalia: Do we assign a male or a female sex-of-rearing?

Clinical algorithms for assigning sex-of-rearing in infants with DSD evolved from ideas developed within the behavioral sciences during the last half of the 20th century. Clinicians accepted these ideas without recognizing that there were minimal outcome data[8]—the clinical psychological model preceded the acquisition of data. Practically, there were minimal outcome data for people with DSD who were *untreated*. Clinical decision making for neonatal assignment of sex-of-rearing in such cases has rested on an unsubstantiated clinical foundation.

What do we know about gender identity and gender role outcomes for children born with DSD? We can say that gender identity outcomes have often been unpredictable or unexpected. Data are insufficient to make very many generalizations. Genetic males with complete androgen insensitivity syndrome (CAIS) always recognize a female identity. Genetic females with congenital adrenal hyperplasia (CAH) almost always[16] (but not in every case)[17,18] recognize a female identity. In two recent reviews of the literature, genetic males with 5α-reductase type II deficiency reared as females made the transition to male gender in about 60% to 70% of the reported cases, usually during or after puberty.[19,20] Discordance between sex-of-rearing and recognized gender sometimes also occurs in genetic males reared as females, including individuals with cloacal exstrophy, mixed gonadal dysgenesis, partial androgen insensitivity syndrome (PAIS), or other conditions, although longitudinal data are incomplete.[18,21]

In general, fetuses exposed to androgens in the face of active androgen receptors (AR) will have some degree (perhaps unpredictable) of brain masculinization or sexual dimorphism.[16,22] Raisman and Field's classic 1971 treatise first noted the presence of cytoarchitectural sexual dimorphism of the brain.[23] Goy and Phoenix delineated some behavioral sexual dimorphisms based on androgen exposure.[24] Numerous clinical studies attest to androgen effects in humans. These sexually dimorphic patterns adapt to influence a child's environment, just as the environment adapts to and influences the child, and later the adolescent and adult. Adequate longitudinal data are unavailable for most DSD conditions.

Decisions about assignment of sex-of-rearing will be made. Parents, social institutions, and historical realities demand it. Without longitudinal clinical evidence, however, clinicians must be prudent in their recommendations to parents and should avoid rigid decision-making algorithms. Using the evidence that is available, and continuing to collect data about the individual child with a DSD for several years, the clinician and parents can be flexible enough to adapt their approaches as they more fully understand the child's self-perception.

It is quite clear that androgen exposure in the face of active AR has a powerful effect on psychosexual development, even if the mechanisms and full spectrum of effects have been only partially delineated. Androgen exposure imprints the brain during critical periods.[25,26] The masculinized brain determines at least a large part of gender-typical behaviors, activities, attitudes, and sexual orientation.[25,27,28] Its effects on gender identity are still being defined.[29,30] Its effects on brain cytoarchitecture, synaptic interconnections, neural pathways, and neurotransmitter functions are becoming increasingly established.[31-33] As new clinical research data become available, the clinical approach to children with DSD can be modified appropriately.[18,30]

DEVELOPMENTAL VULNERABILITIES

Early and multiple hospitalizations create developmental risks and the potential for developmental delays or deficits. A genitourinary diagnosis in the prenatal period is likely to affect the parents in particularly complex psychological ways. Mothers may be more vulnerable to guilt feelings. Both parents are likely to experience anxieties surrounding prenatal or neonatal diagnoses. Neonatal hospitalizations and surgeries impair bonding and engender parental perceptions of an ill or defective child. Marital stresses may proliferate.

Similarly, maternal problems with bonding can lead to infant problems with bonding. The implications and ramifications of such early infancy situations are not all clear. However, disruptions of the typical parent-child relationships are likely to occur. Multiple hospitalizations and chronic illness, along with frequent doctor visits and outpatient procedures, can similarly induce strains in the relationship between parent and child or parent and parent. It is important for the treatment team to recognize that such developmental disruptions may occur. If a child or parent behaves in the medical setting in an inexplicable manner, the treatment team should consider that developmental delays or deficits or misperceptions by the child or parent may be orchestrating the observed reactions.

Because the framework for future development is laid down in the past and present, one must surmise that at least some developmental insults are likely to occur in a child with chronic illness. Development stages may lag or psychosocial stages may be bypassed or delayed to the point of creating long-term psychosocial vulnerabilities. Therefore, it is important to gather an updated psychosocial history in these children at regular intervals. Many children will benefit from a psychosocial rehabilitation program aimed at their specific needs.

PSYCHIATRIC VULNERABILITIES

In addition to vulnerabilities already noted, the urologist needs to be sensitive to the development of major anxiety or mood (affective) disorders in patients. In some cases, anxiety can be pervasive. Disruptive behavioral disorders, relationship disorders, and insults to typical family relationships can also be problematic.

Hospitalization, procedures, and surgeries stress children of all ages. The autonomic nervous system responds to pain, fear, touch, sound, and so on. Blood pressure and pulse, for example, demonstrate obvious changes and effects. The HPA and HPG axes are also likely to endure profound effects that can transform their basic functions and may bias a child's

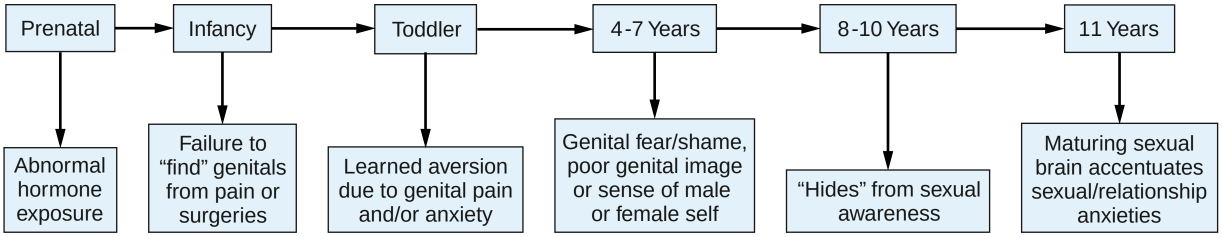
Prenatal
Infancy
Toddler
4-7 Years
8-10 Years
11 Years
Abnormal hormone exposure
Failure to "find" genitals from pain or surgeries
Learned aversion due to genital pain and/or anxiety
Genital fear/shame, poor genital image or sense of male or female self
"Hides" from sexual awareness
Maturing sexual brain accentuates sexual/relationship anxieties

Figure 39-4 Abnormal psychosexual development.

long-term development.[6,34] The disruptions to these axes are likely to lead to stress-sensitive disorders, including anxiety and mood disorders. Anxiety disorders may occur in children without a family history of such disorders and may be involved in the pathogenesis of mood disorders.[6,35]

Disruptive behavior disorders can occur secondary to anxiety disorders, mood disorders, family relationship problems, stress, or social upheaval. Personality factors and vulnerabilities and temperament all play a role in a child's perceptions, comprehension, and reactions. Any combination of these factors can produce effects in a given child. Disruptive behaviors can surface in home life, in academic situations, or in the hospital.

Gender assignment issues at birth influence and stress parenting and the parental relationship. Inappropriate gender assignment can lead to significant gender identity confusion and gender role and peer relationship problems in these children for many years to come.[27,29,30] Some children recognize a gender identity discordant with neonatal assignment. Such self-assignment often emerges between the ages of 6 and 9 years and often after several years of gender identity and role confusion.[8,18] Children who reassign themselves create idiosyncratic existential social difficulties for themselves and for their parents. These children appear to be fairly resilient and do rather well.[8,18] However, parents experience greater turbulence in dealing with such dramatic change in their lives and their child's identity. Past stresses, social realities, guilt feelings, and other adult concerns may create significant coping difficulties.

Genetic females virilized due to CAH and genetic males who are inadequately virilized present a complex and special set of problems. Such children can demonstrate a gender role or behavioral spectrum from very mild to complete masculinization. The prevalence of homosexuality if these children are reared female is probably higher than in the general population.[22,36,37] Additionally, the androgen effects on the brain may strongly influence their attitudes toward sexuality and aggression.[38] These children's behaviors and attitudes can present significant psychosocial and psychosexual developmental difficulties for them and social difficulties for their families. Figure 39-4 depicts some psychosexual developmental difficulties by age in children with genitourinary problems.

PSYCHOLOGICAL AND PSYCHIATRIC INTERVENTIONS

Psychological and psychiatric interventions in children with genitourinary anomalies should address developmental issues. Clearly, the specific treatment strategies must be somewhat individualized. Nevertheless, the following basic algorithm should be helpful.

1. Child psychiatry involvement at the time of diagnosis, to continue longitudinally for the child and the parents
2. Evaluation of psychosocial supports and vulnerabilities
3. Parent education—oral, visual, and written
4. Patient education, appropriate for age and stage
5. Supportive therapeutic interventions as necessary
6. Behavioral interventions as necessary
7. Psychopharmacologic interventions as necessary
8. Referral to regional or national support groups as necessary

Educational Interventions

Family, parent, and patient educational materials can be verbal, written, pictorial, presented by video, or available on the Internet. Access to written materials is extremely helpful to parents and may be the only way to provide accurate information that parents will easily recall. Resources should include age- and stage-appropriate information that will answer general questions while providing a framework for specific questions. Materials for the parents of children who are approaching puberty or already saturated with adolescence should include a realistic appraisal of the child's potential sexual function and fertility and realistic approaches for the achievement of psychosexual developmental milestones.

The child or adolescent requires simple but specific and complete information. Although it can be quite helpful to provide written materials, children and adolescents respond best to face-to-face interactions that are private, frank, and confidential, as appropriate for age. Coping strategies develop only slowly throughout childhood. The psychiatrist and psychologist can educate the parents about coping skills that the parents can then teach gradually to their child. Supportive therapy for self-esteem and sexual self-esteem should be directed to the child. Body image, genital image, acceptance of the genitalia, and self-genital contact may all require strong supportive, intermittent, short-term therapy as the clinical situation demands.

Pharmacologic Interventions

For many psychiatric problems, psychopharmacologic interventions become necessary. Many urologists already use psychopharmacologic preparations—for example, the tricyclic antidepressants (TCAs) such as imipramine (Tofranil). However, few in the pediatric field are aware of the variety of TCAs nor of their full spectrum of uses, side effects, and risks. Child psychiatrists recommend the use of TCAs only after a baseline electrocardiogram (ECG) has been obtained, because of their potential cardiac effects.[39] Effectiveness for enuresis or incontinence has clearly been shown to correlate directly with the serum level; serum levels must be monitored and maintained in the therapeutic range for symptomatic urinary control to be achieved.[40] Additionally, about 5% to 10% of the population are "slow hydroxylators" and will have increased serum levels with a relatively small TCA dose when compared with the general population. These levels may be well into the toxic range for cardiac function in such children. Desipramine, the active metabolite of imipramine, has been associated with sudden death in childhood; nortriptyline has not, and it may have fewer side effects than imipramine while maintaining the same level of therapeutic effectiveness. TCA side effects are to some degree related to serum level.[39] Monitoring of serum TCA levels is crucial, and TCA dosages should be based on the serum concentration.

Because TCAs are known to slow cardiac conduction, the physician should be certain that there is no family history of sudden death, especially in children or adolescents, before initiating TCA therapy. Specifically, an ECG should be obtained before initiation of TCA therapy, again after a therapeutic serum level has been reached, and yearly thereafter. The physician should pay careful attention to the QT/QTc interval. If the interval is 450 msec or longer, then TCA administration should probably be stopped. Liver function tests should be normal before and during TCA administration and should be checked probably every 12 months. Initial TCA dosing should be low because of the sedative and cardiovascular side effects and risks, and the dose should be increased every 4 or 5 days depending on the patient's tolerance of side effects. After two or three dosage increases, the physician should determine the serum concentration. If it is low, the dose may be increased appropriately every 4 or 5 days, continuing this regimen until a therapeutic level is achieved.[39] Constipation and sedation are other side effects of TCA administration.

Other psychopharmacologic agents, such as the stimulants or the SSRIs, have their own therapeutic profiles and risks and benefits for anxiety, mood problems, and disruptive or disinhibited behaviors. The SSRIs, for example, commonly disrupt one or more enzymes in the cytochrome P450 systems, creating risks of toxicity for a variety of other common pharmacologic agents, including some antibiotics, narcotics, and antihypertensives.[41] The delayed orgasm commonly associated with SSRIs may provide a good treatment for premature ejaculation.

Adverse event reports include occasional high-flow priapism with most medications used for attention-deficit/hyperactivity disorder except methylphenidate (Ritalin) but also with sertraline, trazodone, and a number of neuroleptics. Benzodiazepines can be valuable adjuncts for the prevention or treatment of anxiety and agitation related to procedures or perioperative situations. Diazepam (Valium) has a remarkably long half-life; lorazepam is intermediate, oxazepam is short, and midazolam (Versed) is very short. More frequent dosing of shorter-acting preparations reduces the risks of delirium, acute disinhibition ("agitation"), and drug-drug interactions and provides more frequent peak levels, commonly a therapeutic benefit in the postoperative period. It is probably wise to ask for child psychiatric consultation or intervention in children and adolescents treated with psychotropic agents.

Most decongestants and anticholinergics (e.g., oxybutynin) cross the blood–brain barrier and can produce side effects of agitation, anxiety, and hyperactivity. Temperament, language ability, affective vulnerability, and cognitive development interact with such medications, with unpredictable behavioral consequences. Younger children and especially infants and toddlers are quite sensitive to the simultaneous use of multiple psychotropic or psychoactive medications. Postoperative use of narcotics mixed with benzodiazepines and anticholinergic medications can, not uncommonly, lead to delirium. Delirium manifests with agitation, including picking at the clothes and bed sheets, pulling on tubing, and grasping at people's arms or clothes, as well as waxing and waning consciousness or alertness and variable recognition of parents, family, or others. Delirium implies a serious insult to the brain and demands treatment. Treatment in such youngsters usually requires withdrawal of as many psychoactive medications as possible, as soon as possible. The risks of delirium seem to be highest in those children who are already somewhat agitated and intolerant of the restricted activity inherent in many genitourinary surgeries and who must be sedated for medical-surgical reasons.

Behavioral Interventions

For older children and for parents, cognitive behavioral therapy (CBT) can be very helpful as an adjunct to treatment interventions for anxiety, mood problems, self-esteem, sexual self-esteem, and sexual dysfunction. CBT can be useful as an intervention for specific psychiatric and behavioral problems and as a preparatory adjunct to procedures. For adult patients who grew up with genitourinary problems, CBT and insight-oriented therapy may be especially useful and especially appreciated.

For many genitourinary conditions, sex therapy and sex counseling can be very therapeutic. Many of these children and adolescents need to learn to be verbally intimate in order to adapt to the sexual and psychosexual implications of their conditions. Similarly, verbal intimacy can be vital to the ultimate development of sexual intimacy. For the adolescent genitourinary patient, learning verbal intimacy as the initial step in sexual relationships can greatly aid normal psychosexual development and may evolve to more near-normal sexual intimacy. When the urologist discusses with the child his sexual situation, function, and realities, openly and, preferably, alone, the child will benefit clinically and psychosexually and will learn important communication skills about intimate subjects as well. Without such an intervention, many adolescents may face a great obstacle to sexual relationships.

Similarly, children and adolescents with major genitourinary conditions may have to be educated about the importance as well as the function of their own genitalia. They may require education that it is safe to touch or handle their genitalia and that masturbation is a normal activity. Males with significant penile anomalies may require education about sexual positions that permit successful and satisfying sexual intercourse. Some girls with vaginal anomalies may similarly require education. Written and pictorial materials can be very helpful, especially if the treating physician has high levels of embarrassment about frank sexual discussions.

Adults who have endured congenital genitourinary anomalies may require counseling before or during marriage. Interventions for adults may include education about sexual functioning, sexual pleasure, satisfactory sexual intercourse, positions for intercourse, masturbation, verbal intimacy, sexual intimacy, and the importance of intimate activities other than intercourse—touching and sexual touching. Because of improved abilities to cope and to deal with embarrassing and difficult material, adults are likely to require less education and fewer intervention sessions in a given therapeutic approach than children or adolescents.

Children, adolescents, and adults all may require psychosocial habilitation and rehabilitation to develop and adapt despite their significant genitourinary conditions. Major pediatric genitourinary anomalies tend to affect anatomic regions and perceptual areas of such intimacy that few patients are likely to develop and mature without suffering at least some psychosocial insults and psychosexual hurdles. It is essential that the treatment team recognize these vulnerabilities within the patient population in order to provide their patients the best possible overall care, overall prognosis, and outcome.

Table 39-1 **Summary of Some Important Developmental Milestones and Difficulties by Age**

	Prenatal	Infancy	Toddler	4-7 Yr	8-10 Yr	≥11 Yr
Language Development	Neuronal development	Early vocalizations	2- to 3-word sentences	Good vocabulary, *poor* comprehension	Knows when *not* understanding	Good vocabulary and comprehension
Chronic Illness Vulnerabilities	Affects brain development	Brain development, maternal-child bonding affected	Anxiety formation, affective vulnerability	Doctor/hospital anxieties/phobias	Reactive behaviors, demoralization, noncompliance	Mood-anxiety problems vs learning to cope
Psychosexual Developmental Milestones	Spontaneous erections (vaginal lubrication?)	Sensorimotor: finds, stimulates genitals and perineum	Touches/holds genitals, masturbates	Genital "pride," enjoys own nudity	Modesty; interested in others' sexuality	Privacy; active sex fantasies, interest, and expression
Abnormal Psychosexual Development	Abnormal hormone exposure/developmental anomalies	Postsurgery failure to touch or enjoy genitals	Learned aversion due to genital pain or anxiety	Genital fear/shame, poor genital image	Hides sexual interest, poor sense of self as male or female	Maturing sexual brain accentuates sexual/relationship anxieties

CONCLUSION: PRIMACY OF THE CHILD

In summary, genitourinary conditions of childhood and adolescence affect global psychosocial and psychosexual developmental phenomena. It is exigent that the treatment team address "the whole child." Central to this imperative is a recognition of the vulnerabilities that the child or adolescent with genitourinary conditions endures—vulnerabilities within their social, cognitive, academic, and physical realms. The uniqueness of genitourinary problems in children underscores their vulnerability to psychosexual and sexual dysfunction. Children may be confused about issues of identity, urinary and sexual functions, gender identity or role, and relationships. Table 39-1 summarizes some important developmental milestones and difficulties by age.

Prevention as well as preparation of the family and the child for the psychological sojourn that genitourinary conditions and the ramifications of surgical intervention entail can positively affect not only the child's growth and development but also the response to and recovery from medical and surgical interventions. The reduction of anxiety by treatment intervention may help to preclude major lifelong disruptions of the HPA and HPG axes. Because of the prevalence of anxiety and mood disorders in these children, prevention and early treatment would seem paramount.

The concept of the treatment team has never held such importance, nor has it been more critical for the future as we are beginning to comprehend the impact of early trauma on the neurobehavioral development of the child and the child's brain. The modern child and adolescent psychiatrist has a background in anatomy, physiology, molecular biology, and pharmacology that provides unique insights into the developmental, behavioral, and psychiatric vulnerabilities of these children and adolescents. The modern child psychologist has a background in cognitive and behavioral therapies most useful for the child's adaptation and coping, not only with the vagaries of the genitourinary conditions themselves but also with the demands of surgical and medical realities. Psychoneuroendocrinologic implications of these conditions fall within the realm of both psychiatry and psychology. Longitudinal neurobehavioral studies should greatly augment and enhance our understanding of the relationship between malformations, their medical-surgical interventions, and brain development and function.

Finally, the treatment team should design and institute a psychosocial rehabilitation treatment plan for children with moderate or severe genitourinary anomalies and conditions. This plan should consist of an approach for the parents at birth and for the parents and family throughout the child's life. It should include a team approach for age- and stage-appropriate psychosocial adjustments to circumvent or mitigate developmental vulnerabilities during episodes of illness, hospitalization, and surgery. It should incorporate approaches to enhance social competence, social skills, and academic progression. Approaches to the psychosexual development of these children must be a part of this plan. Sexual behaviors and activities must be monitored so that psychosexual developmental interventions can be designed. Developmental goals peculiar to adolescents must incorporate the entire psychosocial rehabilitation plan.

If the treatment team maintains the sense of the primacy of the child, then it can mitigate and ameliorate most of the psychological risks and vulnerabilities of these childhood adversities. The team must design a flexible treatment plan that can be adapted to a specific child's realities as they unfold. Just as the surgeon must adjust to the outcomes of surgical interventions, modifying the treatment plan to improve psychological outcomes can be satisfying and successful.

REFERENCES

For complete list of references log onto www.expertconsult.com

SECTION 2

MALE GENITAL ABNORMALITIES

CHAPTER 40

FORESKIN

Peter M. Cuckow

The foreskin, or prepuce, is a sleeve of skin that covers the end of the penis in its flaccid state; when mature, it may be completely retracted to expose the glans. At birth, it is a piece of skin the size of a large coin, consisting of 3 million cells, 12 feet of nerves, 100 sweat glands, 50 nerve endings, and 3 feet of blood vessels. Its function is to protect the sensitive tip of the flaccid penis, and perhaps its redundancy helps facilitate movement of the penile shaft within the vagina during sexual intercourse. In spite of its diminutive size and simplicity of structure, its removal generates much work for doctors and much controversy in the lay and medical literature. This chapter considers the normal development and function of the foreskin, the so-called abnormalities that are features of this normal development, abnormal development of the foreskin, and its acquired pathologies in children. The surgery of the prepuce, which is principally circumcision, forms the final topic of the chapter.

NORMAL DEVELOPMENT

During its early development, the tip of the genital tubercle, which will subsequently develop into the mature glans, is uncovered. At about 12 weeks of gestation, a fold of skin forms at the base of the glans, which migrates distally to cover it. Initially, this skin fold is more prominent on the dorsal surface, but as it advances, it also migrates ventrally and fuses to form a midline raphe. By 5 months, the glans is surrounded by a sleeve of skin whose inner surface fuses with the outer epithelium of the glans itself.[1] From about 6 months of gestation, a process of keratinization occurs between these two layers, bringing about their separation and depositing a variable amount of keratin between them, often referred to as keratin pearls.[2] This process continues throughout the latter part of gestation.

At birth, it is unusual for the foreskin to be retractable, because of incomplete separation of the epithelial layers and also the conical shape of the foreskin, whose tip is too narrow to permit retraction behind the glans. Only about 4% of newborns have a fully retractable prepuce, and in a further 54% the tip of the glans may be revealed by gentle retraction.[3] Evolution to a fully retractile, widened, and separated foreskin proceeds at a variable rate during childhood. In a study of foreskin development between birth and 3 years of age, Gairdner[3] found nonretractability in 80% of boys at 6 months, 50% at 1 year, 20% at 2 years, and 10% at 3 years. In an older cohort of boys, Oster[4] documented a change from 8% nonretractability to 1% between 6 and 17 years of age. During the same period, glanular adhesions decreased from 63% to 3%, and visible smegma production increased significantly, from 1% to 8% by puberty.

Phimosis, a term derived from a Greek word meaning "to muzzle," is used to describe the narrow, nonretractable foreskin of childhood. Confusion arises because the same term is used to describe a pathologic scarring process at the tip of the prepuce in older children and adults, and for some, it always implies pathology. It is important to distinguish whether the phimosis is primary (developmental or physiologic) or secondary (true or pathologic) to a scarring process such as balanitis xerotica obliterans (BXO). Figure 40-1 shows physiologic phimosis in an infant; the foreskin has been gently retracted to demonstrate its conical shape with a narrow tip. It lacks any scarring, and a normal inner mucosa pouts beyond.

Accumulation of smegma or keratin material beneath the foreskin as it separates varies among individuals. In some, large amounts accumulate in pockets, characteristically in the subcoronal space, and are visible as white lumps or "pearls" beneath the foreskin. These are washed out when complete separation occurs. The resulting space beneath the foreskin can fill with urine during voiding, particularly if its tip remains narrow, prohibiting retraction. Turbulent flow may cause the foreskin to balloon outward, which causes a great deal of concern to the parents but rarely worries the child himself (Fig. 40-2). The condition resolves as retraction becomes complete and can be mitigated in the short term by teaching the child to pull the foreskin back onto the glans during voiding; this eliminates the potential space and aligns the urinary meatus with the open end of the foreskin.

COMPLICATIONS OF A NORMAL FORESKIN

Balanoposthitis

Balanoposthitis is the term for inflammation of the glans and the foreskin seen in boys with nonretractable foreskins. *Balanitis* refers to inflammation of the glans, and *posthitis* to the foreskin component of this common entity. Balanoposthitis occurs in approximately 4% of uncircumcised boys, mostly between 2 and 5 years of age after potty training.[5] The etiology is unclear, and no cause can be identified in many cases, although infection, mechanical trauma, contact irritation, and contact allergy are cited.[6] It is characterized by redness and swelling of the distal penis and prepuce, which is sometimes quite dramatic. This may be associated with discharge into the underpants, and patients may also complain of dysuria, bleeding from the foreskin, and glans ulceration.[5] Rarely, severe symptoms lead to urinary retention.

For the most part, balanitis is a self-limited condition. Various treatments have been tried, including topical and systemic antibacterial or antifungal ointments. Most cases respond to simple bathing, which is best achieved by sitting the boy in a warm bath. This relieves the discomfort and allows him to relax and void. Most patients have only a single severe episode, although recurrent balanitis is said to be a relative indication for circumcision. Acute surgery should usually be avoided, and in particular the dorsal relieving slit of the prepuce. Although balanitis is less common, it is still seen in the circumcised population[7] and therefore is not eliminated by the operation. The decreasing frequency in older boys almost certainly reflects foreskin maturation and the better penile hygiene this affords. There is very little evidence to suggest that balanoposthitis is a precursor to scarring at the tip of the prepuce and subsequent true phimosis.[5]

Paraphimosis

Paraphimosis occurs when the narrow tip of the prepuce is withdrawn behind the glans and constricts the penile shaft, leading to edema of the distal penis (Fig. 40-3). This swelling prevents repositioning of the prepuce over the glans. Complications include urinary retention, ulceration of the glans, and ischemic necrosis of the glanular mucosa. Reduction is usually possible within the first few hours by first reducing the edema of the distal penis. Various techniques have been described, including applying granulated sugar to the penis,[8] adding multiple punctures to the edematous foreskin before compression,[9] and injecting hyaluronidase beneath the narrow band to release it.[10] With this last approach, DeVries and colleagues[10] found that wrapping the distal penis in a gauze swab soaked with saline solution and squeezing gently but firmly for 5 to 10 minutes invariably sufficed to permit reduction without anesthetic. After reduction, the edema subsides. Acute surgery is almost never indicated in this situation. Application of lubricating jelly and local anesthetic creams may be counterproductive in that they decrease the ability to grasp the penis. Later, a circumcision may be offered, but this is not mandatory, because the foreskin will continue to develop normally.

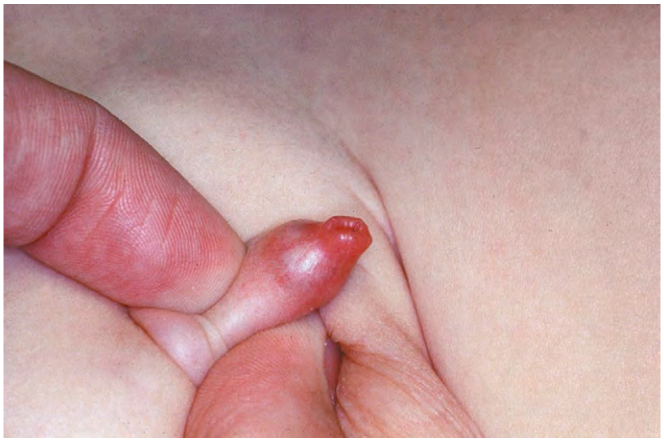

Figure 40-1 The normal foreskin is retracted to show the features of physiologic phimosis. The narrow tip shows no sign of scarring, and the normal inner mucosa pouts beyond.

CONGENITAL AND ACQUIRED CONDITIONS OF THE FORESKIN

The most common developmental anomaly of the penis is hypospadias; in the minor varieties, the abnormality may be confined to a ventral deficiency of the foreskin (Fig. 40-4). Circumcision in these cases results in a "normal" appearance. Abnormal radial distribution of the foreskin around the penis may contribute to torsion of the penile shaft. More minor varieties of this anomaly can be left alone or simply corrected by degloving the penis and redistributing the skin. The more severe rotations (>90 degrees) are associated with dysgenetic bands of tissue at the base of the penis and even inherent abnormality of the penile corpora, which requires a more radical correction.[11]

Penoscrotal Fusion Anomalies

There is a spectrum of anomalies in which there appears to be a lack of separation of the penile shaft skin from the scrotum. The simplest of these is the webbed penis (Fig. 40-5), in which the scrotal attachment extends along the ventral surface of the shaft to a varying extent, and the penis and distal prepuce are otherwise normal. Incision along the line of demarcation between scrotum and penile shaft, with reconstruction of the shaft cylinder and midline closure of the scrotum, achieves a more normal appearance.[12] In more severe variants, the penis is tethered within the deep fascia by abnormal attachments of

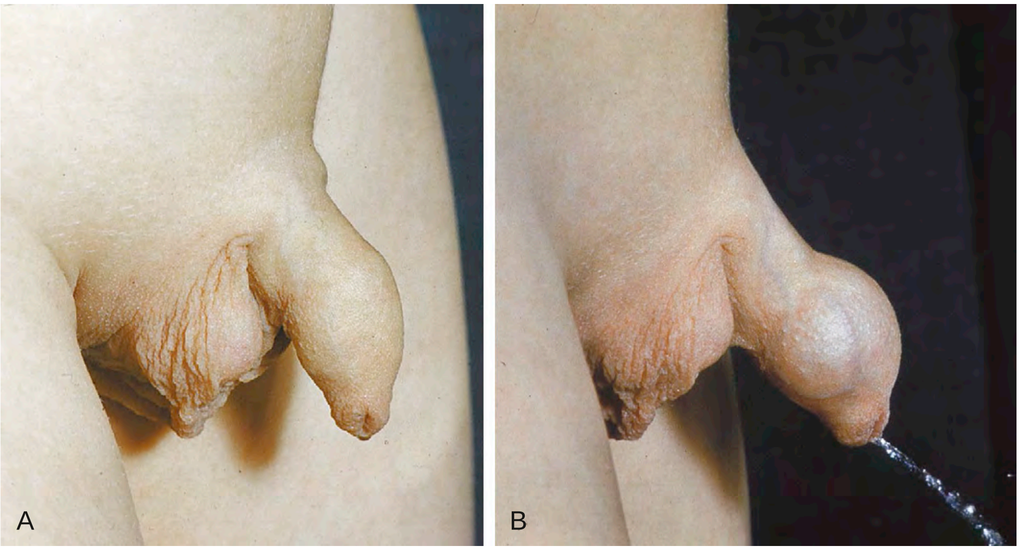

Figure 40-2 Ballooning of the foreskin, before **(A)** and during **(B)** voiding when turbulent urine flow causes distention.

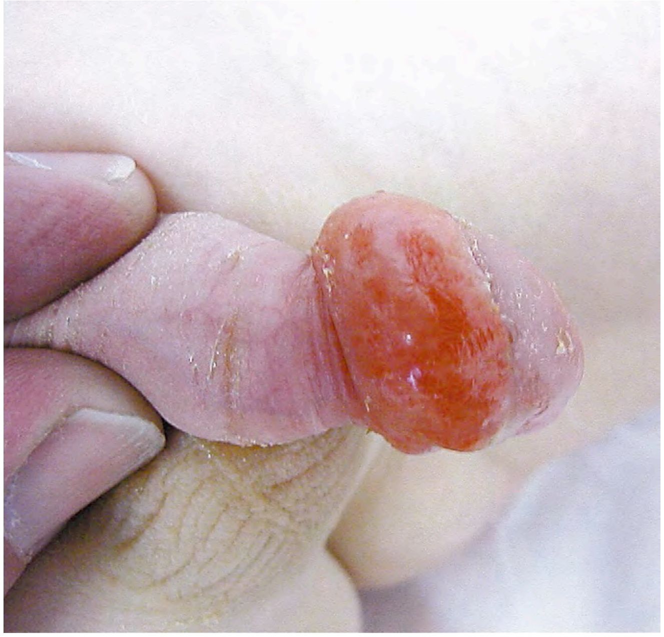

Figure 40-3 Paraphimosis. The narrow preputial tip has been retracted behind the glans, where it obstructs the lymphatic drainage from the end of the penis, which swells. As a result, the foreskin cannot be easily replaced.

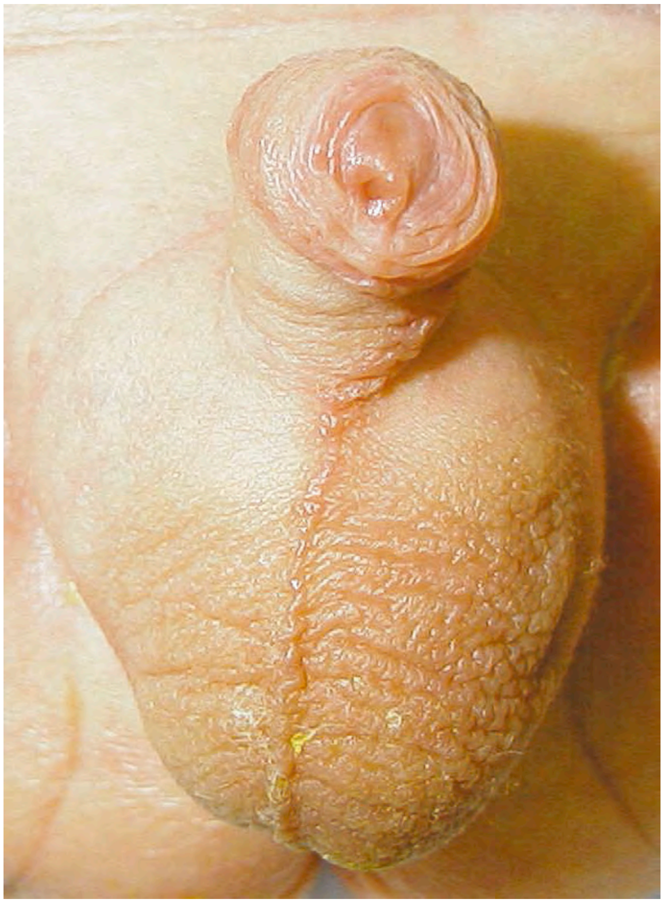

Figure 40-4 A minor form of hypospadias wherein the most obvious abnormality is a ventrally deficient foreskin.

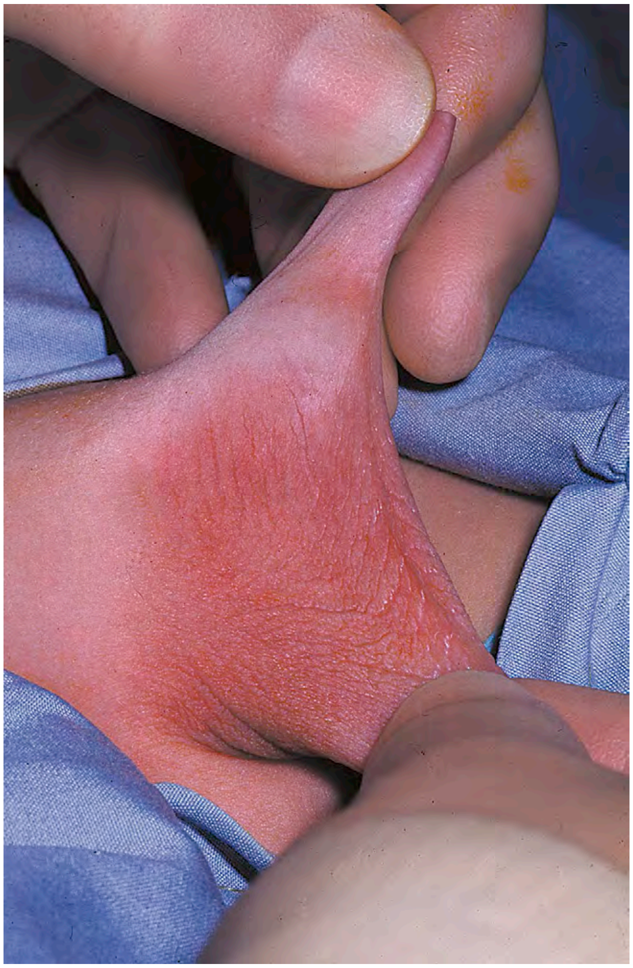

Figure 40-5 Webbed penis. The scrotal skin is fused along the shaft of the penis.

the dartos, the fusion of scrotum and shaft skin extends more distally, and the impression may be that of a micropenis.[13] In fact, the penis is of a normal size and is simply *concealed*, *buried*, or *hidden* (all terms used to describe the anomaly). A buried penis is readily confirmed by careful examination with palpation through the prepubic tissues. In some cases there is a physiologic phimosis at the preputial meatus and a very capacious inner preputial sac, which has been termed the *megaprepuce*. This balloons dramatically during voiding and empties by dribbling.

Many operations have been described for correction of these more severe fusion anomalies, and most authors agree that simple circumcision is contraindicated.[14] Release of the penile shaft from its restricting deep attachments to prevent reburying is well recognized, but there is variation in the approach to providing its skin cover. Use of a tailored inner preputial sleeve[15] or a rectangular island flap of inner mucosa[16] has been described, but neither technique gives a normal circumcised appearance. As with the simpler webbed penis, the line of demarcation between scrotal and shaft skin can be demonstrated, suggesting that a similar surgical approach can be taken.[12,17] Incision along this line and deep dissection to the penile root release the shaft and unfurl the redundant inner prepuce. Removal of the inner prepuce leaves a rectangle of skin that is sufficient to provide cosmetic skin cover and the appearance of circumcision. The scrotum is closed in the midline, giving it a more caudal appearance. This technique

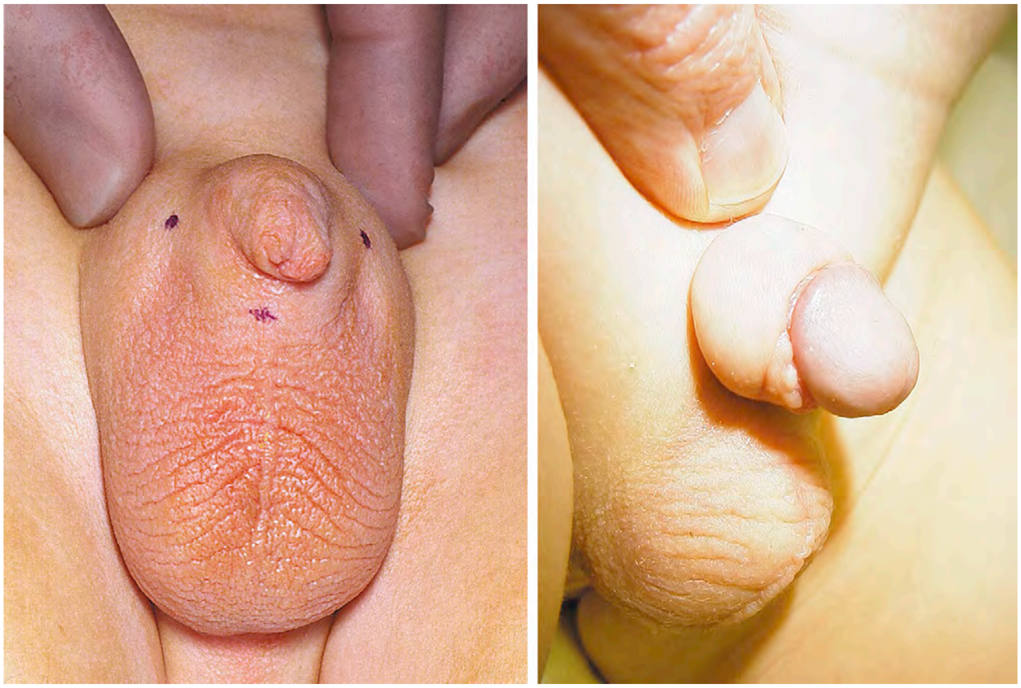

Figure 40-6 Buried penis. *Left,* The scrotal skin and penile shaft skin have failed to separate. The penile shaft is tethered to the deep fascia. There is a phimosis and a large inner preputial sac, which balloons during micturition. *Right,* Same patient, after surgical correction.

has been successfully applied to more than 20 boys with good cosmetic results and no recurrent burying (Fig. 40-6).[18]

Penile Lymphedema

Primary lymphedema of the prepuce is a rare condition caused by abnormal development of the lymphatic drainage of the genital skin (Fig. 40-7). The skin is thickened with chronic edema, whereas the underlying glans and corpora are usually unaffected. In rare instances, the edema regresses spontaneously, but surgery, consisting of circumcision and removal of the bulky subcutaneous tissue, gives reasonable results.[19] An alternative approach is to excise all the affected skin and subcutaneous tissue and reclothe the penis in split-skin grafts.[20,21] Secondary lymphedema is more common, and worldwide the most common cause is filarial infection in the tropics.[22] Other causes include trauma, previous penile surgery,[23] a redback spider bite,[24] and an extraintestinal manifestation of Crohn disease.[25,26] In the last example, the genital manifestations may predate overt bowel symptoms, but a high index of suspicion and persistence will eventually lead to the underlying diagnosis. Urethral involvement may complicate the management of this difficult clinical problem.[26]

Trauma

Injury of the prepuce is uncommon, and physicians should be alert to the possibility that it may be nonaccidental. In a survey of 32 foreskin injuries, the mechanism seen most commonly (in 6 boys) was a zipper injury.[27] The foreskin can be easily released if the zipper is cut close to the point of its entrapment, enabling it to be pulled apart easily.[28]

Balanitis Xerotica Obliterans

The infiltrative skin condition BXO, also known as lichen sclerosus et atrophicus, is the cause of true phimosis and a clinically recognizable lesion at the tip of the prepuce.[29] It is said to be a common underlying cause of persistent nonretractability of the foreskin at puberty,[4] although the overt lesion is rarely seen in children younger than 5 years of age.[30] Patients present with inability to retract the prepuce, discomfort after micturition, and occasional minor obstructive signs.[31] Figure 40-8 demonstrates the typical appearance of a white, sclerotic tip to the prepuce and no normal inner prepuce pouting beyond on attempted retraction. There may be similar changes on

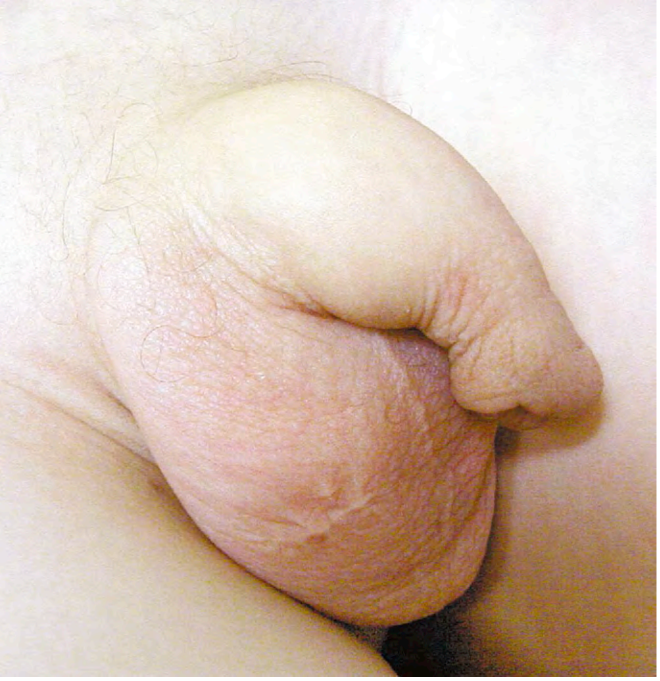

Figure 40-7 Primary penile lymphedema. The underlying shaft and glans are normal.

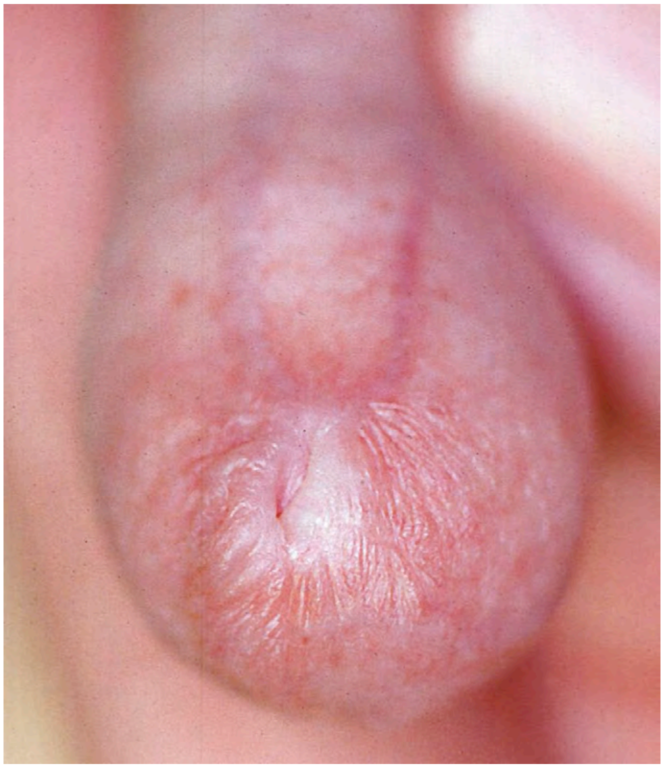

Figure 40-8 Balanitis xerotica obliterans. There is recognizable scarring at the tip of the prepuce and no pouting inner mucosa (compare Figure 40-1).

the glans itself, and the meatus can be involved in the scarring process, resulting in meatal stenosis. Rickwood and coworkers[30] reviewed 23 patients operated on for clinically diagnosed true phimosis and found that 21 had histologically proven BXO with thickening, edema, and lymphocytic infiltration of the dermis. The etiology of BXO is unknown, but it may be of viral origin.

It is unclear whether the lesion of BXO responds to the local application of steroid creams, because many patients with physiologic phimosis have been included in most studies. Lindhagen[32] compared steroid cream with placebo in patients with nonretractable foreskin and showed that all of the failures had histologically proven BXO. The operative management is circumcision, which removes all the affected tissue in most childhood cases. One series of 10 boys monitored for 5 years after circumcision showed no recurrence or regression of glanular lesions,[33] although BXO is often cited as a precursor to postcircumcision meatal stenosis.[34] Authors vary on this association, and different series of patients with meatal stenosis have shown either 10 of 12 patients with previous BXO[35] or, in contrast, 0 of 12 patients previously affected.[36] In the context of hypospadias and other urethral conditions, the urethra and glans may be severely affected. In such cases, the condition poses an extra difficulty in achieving a satisfactory long-term result of reconstruction.

SURGERY OF THE FORESKIN

Indications for Circumcision

Globally, most circumcisions are performed for religious reasons and are a fundamental part of the Jewish and Muslim faiths. Jewish boys are circumcised on the eighth day of life, and Muslim boys are usually circumcised during childhood. In addition, many boys are circumcised shortly after birth, particularly in the United States, for cultural reasons or through the preference of their parents. In most American cities, the neonatal circumcision rate is approximately 90%.[37] In contrast, in Scandinavian cultures, circumcision is avoided if at all possible, and the rate there is the lowest in the Western world.[38]

Contraindications for circumcision should include hypospadias (unless it is part of the reconstructive procedure), buried penis, and any medical condition that increases the risks of the procedure (e.g., a bleeding diathesis).

The justification for routine neonatal circumcision has created a wealth of discussion, and many “scientific” arguments have been raised to support this practice. In childhood, circumcision leads to a reduction in the incidence of foreskin-related problems, but they can still occur (6%, compared with 14% of uncircumcised boys[7]). A study of a birth cohort of 500 boys from New Zealand demonstrated a similar incidence of foreskin complaints in childhood regardless of whether circumcision had been performed.[39]

The finding of a 10-fold increase in urinary tract infections among uncircumcised infants,[40] backed by an impressively large patient review,[41] suggested a protective effect through reduction of the periurethral carriage of pathogenic organisms.[42,43] Critical assessment of the risks has shown that approximately 100 prophylactic circumcisions would be needed to prevent one urinary tract infection, and, given that the incidence of renal scarring after febrile urinary tract infection is 10% to 20%, up to 1000 circumcisions would have to be performed to avoid one renal scar.[44] This large number of “unnecessary” operations is hard to justify, particularly in view of the potential complications (see later discussion). There remains, however, a strong argument for prophylactic circumcision in the cohort of boys with a prenatally diagnosed uropathy, for whom urinary tract infection represents a more significant risk.[45] In addition, it is the anecdotal experience of many pediatric urologists that circumcision of patients with severe uropathy and breakthrough infections may prevent further infective episodes.

The more common problems of the foreskin listed previously (physiologic phimosis, balanitis, ballooning, and paraphimosis) are related to its normal development and do not represent absolute indications for circumcision in childhood. A general lack of understanding of this process and incorrect diagnosis are apparent when referral patterns are studied. In three papers from pediatric surgical units in the United Kingdom, only 23% to 28% of boys referred were offered surgery after critical assessment by a specialist.[46-48] It is likely that other units with less strict criteria are performing many unnecessary circumcisions.[47] The most clear indication for childhood medical circumcision is BXO, but this accounts for only a small proportion of the circumcisions performed in the United Kingdom on medical grounds. Currently, it is estimated that up to 21,000 “medical” circumcisions are performed annually in the United Kingdom, and 6% of boys are circumcised by their 15th birthday.[47]

Circumcision Techniques

Neonatal circumcisions are usually performed with the patient under local anesthesia with a clamp or Plastibell device.[41,49] With the Gomco clamp, the foreskin is retracted, congenital preputial adhesions are separated, and the appropriate-sized bell of the clamp is placed over the glans. The foreskin is replaced over the bell, and the clamp is assembled. Closure of the clamp crushes the skin, allowing the distal prepuce to be excised and producing a suture-less anastomosis just below the corona. The Plastibell is similarly placed over the glans, and the foreskin is replaced over it. A suture is tied around the foreskin, crushing it against a groove on the outer circumference of the device, and the distal foreskin is excised. The bell remains in situ until skin necrosis allows it to separate and fall off, after a mean of 9 days.[50] In the meantime, the infant voids through the open end of the bell. Jewish ritual circumcisions are usually performed with a Mogen clamp. This has a slit through which the foreskin is pulled and then crushed above the glans. The distal foreskin is excised before the inner prepuce is retracted, and a circumferential dressing is applied.[51,52]

In older children, it is usual to perform circumcision under general anesthesia with the addition of a local anesthetic penile or caudal block to provide good analgesia during and immediately after the operation.[34] Although larger sizes of the clamp devices are available, most circumcisions are performed by the freehand or sleeve techniques. For the freehand technique, the foreskin is held in clips, and a dorsal slit made with scissors to just below the corona. The incision is carried forward on both sides to the frenular aspect of the penis, leaving a cuff of inner prepuce below the glans. The edges are separated, and hemostasis achieved with bipolar diathermy or absorbable ligatures. The edges are then opposed with interrupted absorbable sutures. In the sleeve technique, the foreskin is retracted and a circumferential incision is made in the inner prepuce, 0.5 cm below the glans. The foreskin is replaced, and a matching outer incision is made at the level of the corona. The sleeve of skin between the incisions is then removed, hemostasis is achieved, and the operation is completed as for the freehand technique.

Circumcision Complications

Given the prevalence of circumcision, any complication of the procedure, however uncommon, will affect a significant number of patients. A wide range of complications is reported, although there are few prospective long-term studies. Historically, there have been significant numbers of deaths following the procedure, due to anesthesia, hemorrhage, and infection.[3] Although these are extremely rare in modern medical practice, death is still a feature of ritual circumcision in the Third World.[53]

Early complications include hemorrhage (0.04% to 20%), retention of urine (0.02% to 43%), infection (0.5% to 12%), and meatal ulceration (0% to 31%). Ulceration is more often seen after neonatal circumcision, because of the increased vulnerability of the meatus in the diaper-wearing age group. It is followed by meatal stenosis in 26% to 38% of cases.[34,38,50,54-60]

Meatal stenosis (Fig. 40-9) is the most significant long-term complication, reported in 0% to 11% of cases. It manifests with pain on initiation of micturition, a narrow high-velocity stream, and, occasionally, bleeding after micturition.[36] It is managed by meatoplasty. Other long-term complications are harder to define. Cosmetic appearance is subjective, but significant numbers of unsatisfactory outcomes are alluded to by papers on revision circumcisions.[61] Removal of too little skin can result in an annular scar at the tip and a true phimosis that conceals the glans.[62] Removal of too much skin may require grafting, but usually a satisfactory outcome is achieved if the shaft is left to granulate.[51]

Small numbers of patients with other significant problems have been the subject of case reports in the literature. Complete loss of the penis (usually associated with monopolar diathermy and coagulation of the corpora), amputation of the glans, and damage to the urethra leading to a fistula are all reported.[63] The overall complication rate is reported to be between 0.06% and 40%, and the rate of reoperation is between 0.04% and 14.5%.[34,38,50,54-60]

As discussed previously, there is a great range of complication rates reported in the literature. In particular, there seems to be a difference between neonatal circumcisions (mostly from the United States) and those performed in older boys (from Europe and Australia). The differences are highlighted in Table 40-1. Whereas the complication rate seems much lower after neonatal circumcision, large numbers of operators are involved, and the method of data collection is retrospective, with little formal follow-up and reliance on scant medical records. By comparison, the series in older boys are smaller

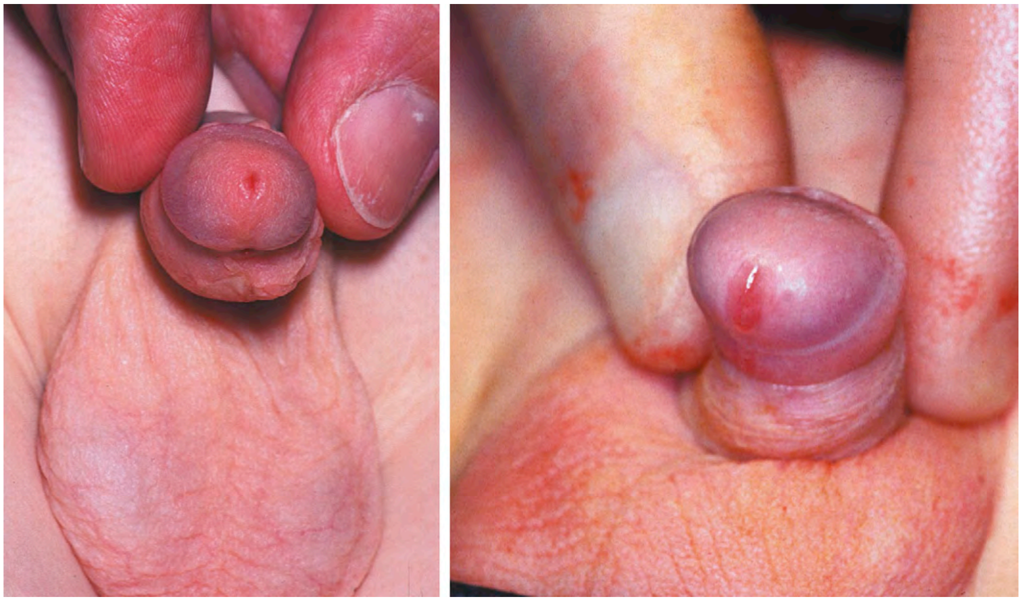

Figure 40-9 Meatal stenosis. A narrow meatus after circumcision *(left)*, compared with a normal meatus in an uncircumcised boy *(right)*.

Table 40-1 Meta-analysis of the Complications of Circumcision in Various Settings

	Neonatal Circumcisions (U.S.)[54,56,57]	**Neonatal Circumcisions (Patel)**[55]	**Circumcisions in Childhood (Europe, Australia)**[34,38,50,58-60]
No. of patients	116,841	100	1192
Type of study	Retrospective	Prospective	Prospective
Hemorrhage (%)	0.4	4	7
Infection (%)	0.16	8	4.3
Unsatisfactory circumcision (%)	0.15	5	2.1
Meatal stenosis (%)	—	8	5.1
Reoperation rate (%)	0.17	>2	5.0
Overall complication rate (%)	0.72	>35	20.1

and from small groups of surgeons performing audit, which is often prospective. It is clear that when such an approach is applied to neonatal circumcision, as in Patel's series[55] from Canada, the complication rates are similar. Because it is such a commonplace operation, even low complication rates imply a significant number of affected individuals.[63]

Preputial Plasty

Although the best way to avoid the complications of circumcision is not to perform the operation, simpler foreskin-preserving techniques have been proposed. Preputial plasty, which widens the narrow preputial tip, is advocated as an effective way to produce a retractable foreskin that has few complications.[60] Various techniques have been described, the simplest of which involves a longitudinal dorsal incision in the tight phimotic band.[64] This is deepened to the level of Buck fascia and then sutured transversely with absorbable sutures.[60] Providing the foreskin is mobilized early, the results have been good, and complications are few compared with those of circumcision.[60,65] Modifications of this basic technique have been proposed, including multiple smaller plasties to achieve a better cosmetic outcome.[66-68] Undoubtedly, the procedure works best on a normal prepuce—which perhaps should be allowed to continue to develop normally.

REFERENCES

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CHAPTER 41

HYPOSPADIAS

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> My brain, it's my second favorite organ.
>
> —Woody Allen

DEFINITION AND ANATOMY

Hypospadias can be defined as incomplete virilization of the genital tubercle that causes an insufficient development of the tissues forming the ventral aspect of the penis.

Three associated anomalies are classically found in the hypospadiac penis: (1) an ectopic opening of the urethral meatus located at any place between the glans and the base of the penis, (2) a ventral curvature of the penis (chordee), and (3) a hooded foreskin with a marked excess of skin on the dorsum of the penis and a lack of skin on the ventrum. In fact, the chordee and the hooded foreskin are not constant, and a hypospadiac meatus may be found under a normally formed prepuce. Chordee may occur in isolation, without an ectopic urethral opening, but it is often associated with a hypoplasia of the corpus spongiosum.

Anatomically, this anomaly includes the following characteristics, from the tip to the base of the ventral aspect of the penis (Figs. 41-1 and 41-2):

1. The glans opens ventrally.
2. A segment of urethral tube of variable length is missing and is replaced by a urethral plate extending from the ectopic meatus up to the glans cap, between the two corpora cavernosa.
3. There is a hypoplastic length of the tubular urethra that is not surrounded by any corpus spongiosum; often, it is covered by a thin layer of skin stuck tightly on it.
4. The division of the corpus spongiosum (Fig. 41-3) is always proximal to the ectopic meatus (and sometimes several centimeters behind the ectopic meatus) in two pillars that extend laterally up to the glans cap in a fan-shaped position; this division of the corpus spongiosum is often outlined on the ventral skin by a small cutaneous ridge.
5. Proximal to the division of the corpus spongiosum, all of the structures forming the ventral aspect of the penis are normal.
6. The frenular artery is consistently missing.
7. The dorsum of the penis is normal.

It appears from these simple observations that the division of the corpus spongiosum marks the proximal landmark of the malformation. The preputial hood is the direct consequence of the ventral triangular defect. The summit of the triangle is the division of the corpus spongiosum, the two sides are represented by the two lateral pillars of spongiosum, and the glans plate is its basis. At the time of surgery, it is easy to delineate this triangle by drawing two lines along the cutaneomucosal junction of the prepuce on each side (Fig. 41-4). Where the two lines cross is where the corpus spongiosum splits.

The chordee itself is a direct consequence of the abnormal proximal division of the corpus spongiosum and the subsequent hypoplasia of the ventral tissues sitting in the triangular defect. Chordee is related to (1) the tethering of the ventral hypoplastic skin onto the underlying structures (urethra) in most cases; (2) the fan-shaped lateral and upward extension of the divided corpus spongiosum; (3) the tethering of the urethral plate and the hypoplastic distal urethra (not surrounded by any spongiosum) onto the corporeal surface; and (4) in rare cases, an asymmetric development of the corpora cavernosa.[1,2]

Many classifications of hypospadias have been published, mainly based on the position of the ectopic meatus, which is an insufficient criterion to define the severity of this malformation. The following classification is based on the level of division of the corpus spongiosum and is of practical help when deciding which surgical procedure to use[3]:

1. Glanular hypospadias (Fig. 41-5). The ectopic meatus sits on the glans tissue behind the normal site. Although these cases may look quite minor, they can be associated with a marked hypoplasia of the distal urethra and a glans tilt or chordee. These hypospadias cases are often tricky to repair, because parents' expectations are high and surgical techniques are not entirely satisfactory. The meatus may look very tight but is rarely causing any urine flow obstruction.
2. Hypospadias with a distal division of the corpus spongiosum associated with little or no chordee (Fig.41-6).
3. Hypospadias with a proximal division of the corpus spongiosum associated with chordee (Fig. 41-7). Paradoxically, these cases are often simpler to handle because surgical techniques to correct the chordee and reconstruct a long length of urethra are well established.
4. Hypospadias cripples. These are patients who have already undergone several procedures that failed, leaving them with scarred tissues, an abnormal meatus, strictures, urethral dehiscence, fistulas, and, of course, bad cosmetic and psychological results.

There are definitely no categories of "minor" and "major" hypospadias. All hypospadias cases are surgical challenges with a significant number of complications even in the best hands.

Embryologically, hypospadias results from a failure of tubularization of the horizontal segment of the urogenital sinus, which occurs during the 11th week of gestation for the penile urethra and during the 4th month of gestation for the glanular urethra.[4,5]

INCIDENCE AND ETIOLOGY

The incidence of hypospadias has increased over the past 15 years in Western countries.[6] There is approximately 1 hypospadias for every 250 male births. The incidence is even higher if there is a family history of hypospadias (1 in 100 to 1 in 80 male births).[7]

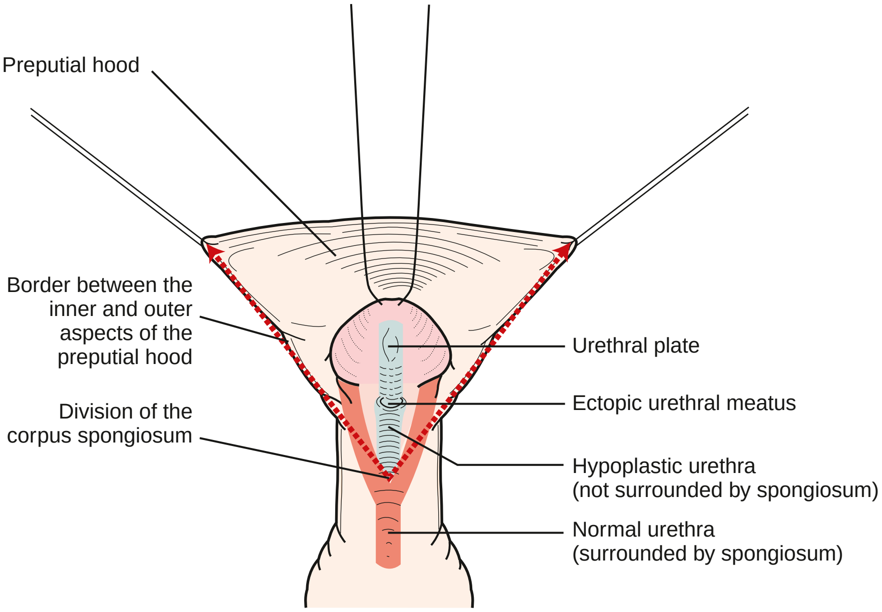
Preputial hood
Border between the inner and outer aspects of the preputial hood
Division of the corpus spongiosum
Urethral plate
Ectopic urethral meatus
Hypoplastic urethra (not surrounded by spongiosum)
Normal urethra (surrounded by spongiosum)

Figure 41-1 Anatomy of the ventral radius of the penis. There is a triangular ventral defect, with its summit at the division of the corpus spongiosum and its base at the glans cap.

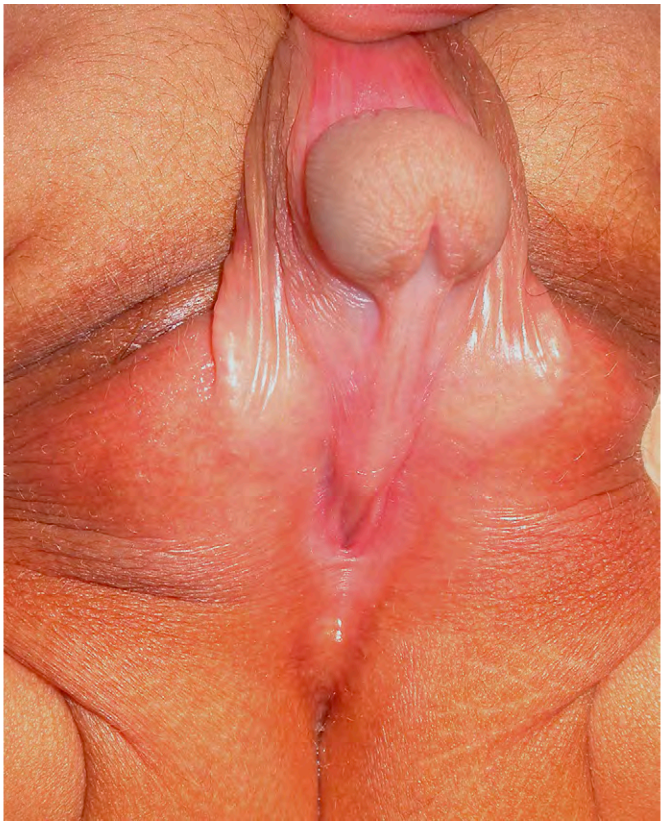

Figure 41-2 Severe hypospadias with proximal division of the corpus spongiosum and chordee.

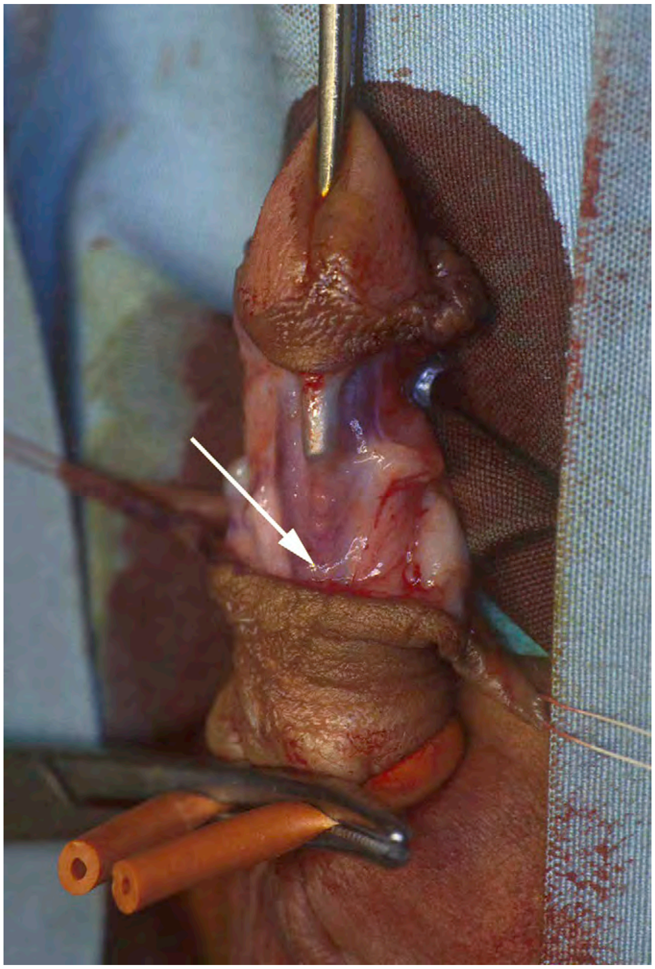

Figure 41-3 Midshaft division of the corpus spongiosum (*arrow*). The distal urethra is hypoplastic (not surrounded by spongiosum). The urethral meatus is almost at the right place. This illustrates that the position of the meatus is a poor criterion of severity compared with the level of the division of the corpus spongiosum.

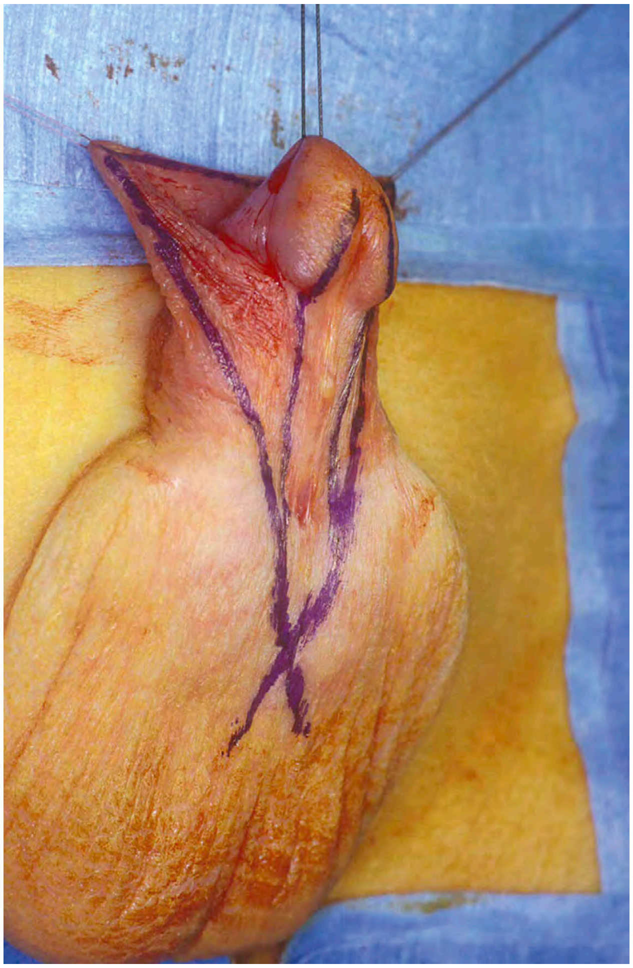

Figure 41-4 To identify the level of division of the corpus spongiosum, a line is drawn on each side along the border between the inner and outer aspects of the preputial hood. Where the two lines cross is the division of the corpus spongiosum.

Four main protagonists might be involved in the male genital construction (Fig. 41-8):

1. The child himself, with his gene bank, his endocrine machinery mainly represented by his gonads supervised by central hormonal control, and his target tissues with their protein platforms which may or may not respond to endocrine stimulation
2. The placenta, with its complex endocrine machinery, which orchestrates the hormonal climate, especially during the first part of gestation, and performs other functions not fully understood and evaluated
3. The mother, with her own hormonal production and its possible disorders that may affect the development of the child
4. The environment of the child and the mother, which may also interfere with this fine balance.

Disruptors and promoters may interact in this complex play in which many other unidentified agents may also have a role.

The place of hypospadias on the palette of disorders of sex development (DSD) is not completely clear. In the past, isolated hypospadias was distinguished from male pseudohermaphroditism. This separation is no longer valid, and it is likely that this congenital malformation belongs to a spectrum of errors in which endocrine disorders may have only a limited part. Very little is known about the "ground workers," those molecular agents such as tissue proteins, growth factors, vascular factors, and tissue destructors (apoptosis), which need to be well balanced to establish an equilibrium between constructive and destructive factors.

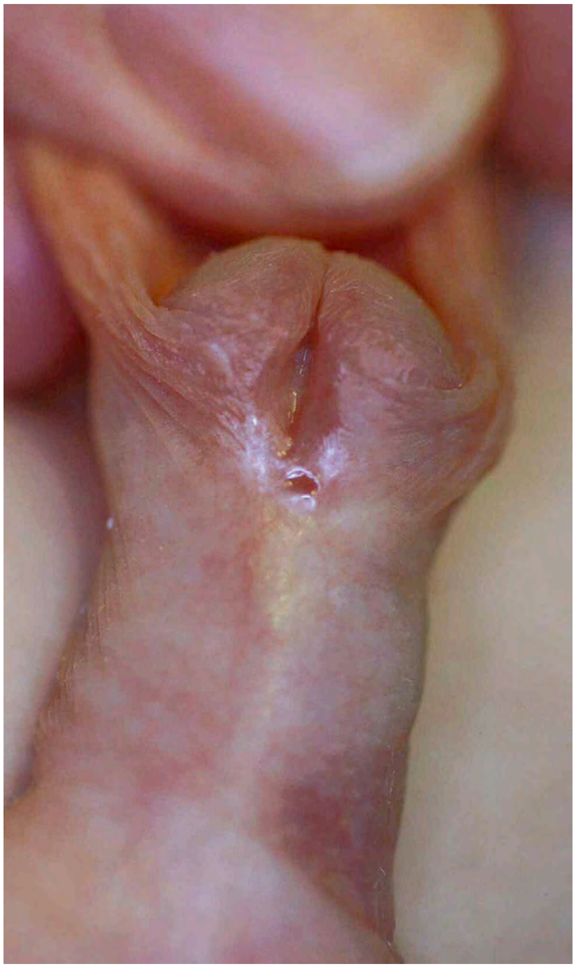

Figure 41-5 Glanular hypospadias.

The Genes

Among the genetic disorders affecting the child and his genital construction, two groups can be distinguished: the isolated gene mutations and the syndromic genetic disorders (Table 41-1).

In a series of 205 hypospadiac patients compared with 205 controls, the risk of having another child with hypospadias was 17-fold.[7] In a Swedish series of 2500 patients, 7% reported at least one additional family member with hypospadias.[8]

The Hormones

In a 1997 report,[9] defects of the testosterone biosynthetic pathway in boys with hypospadias determined the incidence of defects in three major enzymes (3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, and 17,20-lyase) in 30 boys with fully descended testes but with proximal hypospadias. One half of the boys had evidence of impaired function of one or more of these enzymes, suggesting that there was an underlying defect in the biosynthesis of testosterone. This paper surprised many, and another study screening 32 consecutive hypospadias patients did not confirm the same findings.[10]

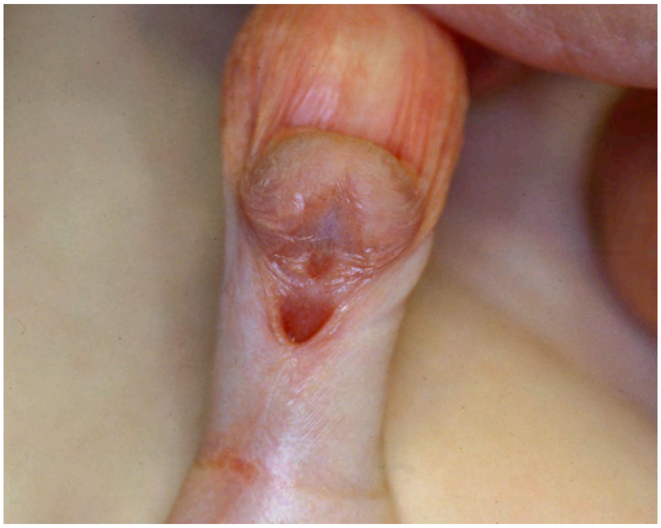

Figure 41-6 Anterior hypospadias with a distal division of the corpus spongiosum.

Shima and colleagues showed that the more severe the hypospadias was, the less satisfactory was the response to stimulation by human chorionic gonadotropin (hCG).[11] Here again, this was not found in Feyaerts and associates' paper.[10]

Mutations of the androgen receptor are rarely found in hypospadias.[12]

In total, fewer than 5% of hypospadias patients have an identified endocrine disorder, although it is most likely that some hormonal impairment occurred during gestation and led to the insufficient virilization of the genital tubercle.[13]

The Placenta

The placenta probably plays a major role in virilization of the genital tubercle during the first part of gestation. Fredell and colleagues[8] examined discordant monozygotic twins and found that the birth weight of the twin with hypospadias was significantly lower than the birth weight of the twin without hypospadias.[14-16] Another study found that boys with hypospadias had a lower placental weight than control boys.[17] Hypospadias is also more common with mothers who are very young or relatively old.[18] In these groups of pregnant women, the placenta is often less developed. These findings clearly point out the essential role of the placenta in genital construction, although very few markers can attest to this hypothesis.

Growth Factors and Protein Balance

Other research studies showed that epidermal growth factors may be lacking on the ventral radius of the penis.[19] In the study of El-Galley and colleagues,[19] the mean epidermal growth factor value was low in skin adjacent to hypospadias defects compared with normal phallic skin, suggesting that inadequate expression of epidermal growth factor may be related to the etiology of hypospadias and to possible wound complications after surgical treatment of hypospadias. Some clinical and experimental studies are currently underway to introduce these missing factors after hypospadias surgery, with a goal of improving the quality of healing.[20]

A recent study performed by Morera and coworkers[7] showed that the balance between structuring (claudin 1) and destructuring proteins was impaired in hypospadias patients with an excess of enzyme activity (metalloproteinase 2) on the ventral aspect of the penis, compared with controls or with the dorsal tissues of the penis. This could be either the cause or the consequence of the insufficient formation of the tissues sitting on the ventral aspect of the penis. Vascular growth factors are also being studied and could affect the development of the ventral radius of the penis (Fig. 41-9).

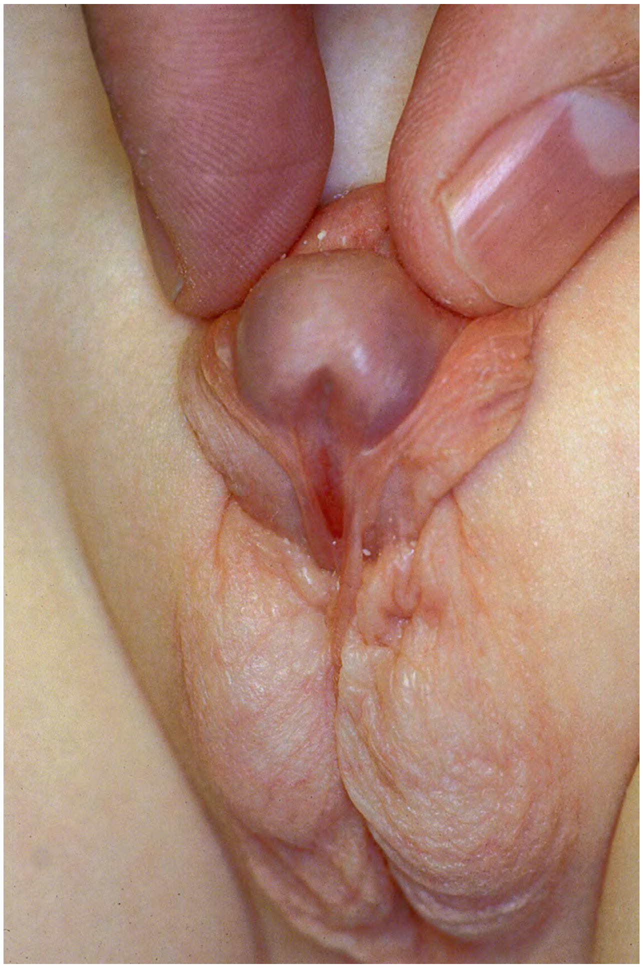

Figure 41-7 Severe perineal hypospadias.

Environmental Promoters and Disruptors

Environmental factors may play a role in the etiology of hypospadias and could explain the worldwide increase in its incidence. These factors are mainly represented by estrogens or estrogen-like substances (plant and fungal estrogens such as soya) in the drinking water, pesticides (e.g., dichlorodiphenyltrichloroethane [DDT]), and other toxic substances (e.g., polychlorinated biphenyls [PCBs]), which are known to disrupt reproduction—the so-called endocrine disruptors.[21-24] Experimental data in animal models support the hypothesis that maternal exposure to endocrine disruptors causes hypospadias in the fetus.[25] Activating transcription factor 3 has been shown to be elevated in humans with hypospadias and to be regulated by estrogenic compounds. It may be that environmental endocrine disruptors act at the genetic level to disrupt activating transcription factor 3, resulting in hypospadias.[26]

In total, the cause of hypospadias remains essentially unknown and is likely to be multifactorial, with a critical period at the beginning of gestation, when the genital tubercle differentiates.

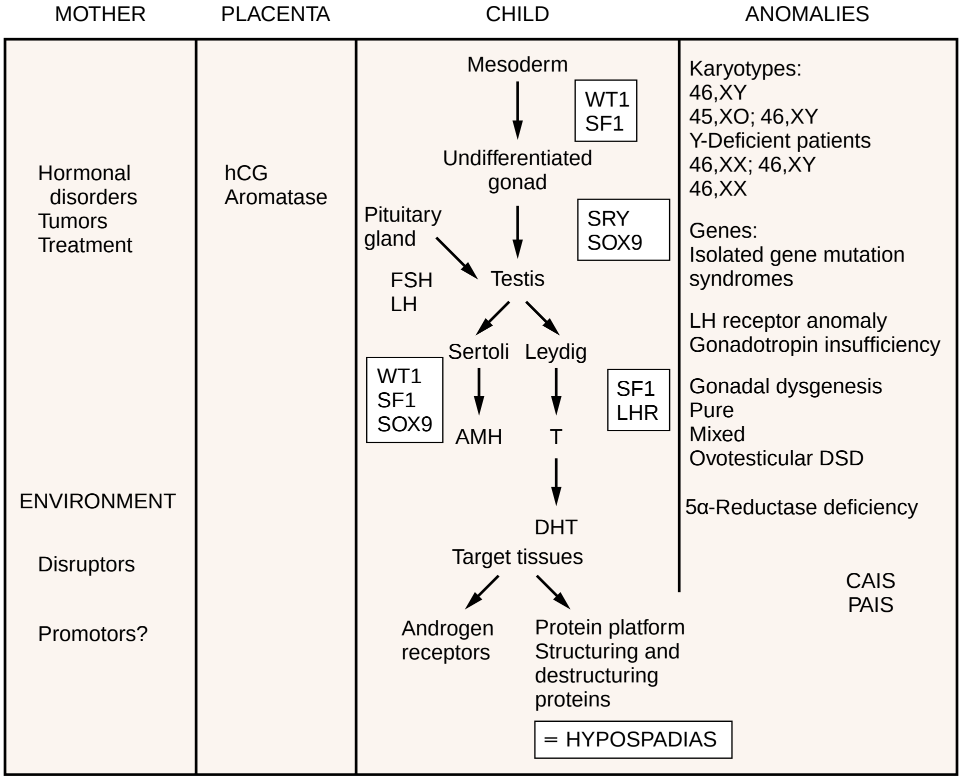
MOTHER
PLACENTA
CHILD
ANOMALIES
Hormonal disorders
Tumors
Treatment
ENVIRONMENT
Disruptors
Promotors?
hCG
Aromatase
Mesoderm
WT1
SF1
Undifferentiated gonad
SRY
SOX9
Pituitary gland
FSH
LH
Testis
Sertoli
Leydig
WT1
SF1
SOX9
SF1
LHR
AMH
T
DHT
Target tissues
Androgen receptors
Protein platform
Structuring and destructuring proteins
= HYPOSPADIAS
Karyotypes:
46,XY
45,XO; 46,XY
Y-Deficient patients
46,XX; 46,XY
46,XX
Genes:
Isolated gene mutation syndromes
LH receptor anomaly
Gonadotropin insufficiency
Gonadal dysgenesis
Pure
Mixed
Ovotesticular DSD
5α-Reductase deficiency
CAIS
PAIS

Figure 41-8 The main protagonists that might be involved in male genital construction leading to hypospadias. AMH, anti-müllerian hormone; CAIS, complete androgen insensitivity syndrome; DHT, dihydrotestosterone; DSD, disorders of sex development; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; PAIS, partial androgen insensitivity syndrome; T, testosterone.

Table 41-1 Examples of Gene Mutations Associated with Hypospadias

Isolated Gene Mutations
SRY
DAX1 (Xp21)
WNT4 (1p35)
DMRT1 and *DMRT2* (9p24.3)
Chromosomic deletions (2q32.1-35 and 10qter)
Syndromic Gene Mutations
SF1 (no adrenal glands—low maternal estradiol)
WT1 (abnormal kidneys)
Denys-Drash syndrome (Wilms' + renal failure)
WAGR syndrome (Wilms' + aniridia + mental retardation)
Frasier syndrome
SOX 9
HOXA13 (hand-foot-genital syndrome)

HISTORY OF HYPOSPADIAS SURGERY

One of the first descriptions of hypospadias was by Galen in the 2nd century A.D. He clearly described the problem of infertility associated with a proximal meatus and penile chordee, and he was the first to use the term "hypospadias." Antyl described the first surgical repair during this period: his technique involved amputating the penis distal to the meatus, a method probably not acceptable today! After this early work, little was added to our understanding of hypospadias and its treatment until the second half of the 19th century, when most of surgical techniques employed today were first described.

The modern principles of hypospadias surgery were well described in the mid-1800s, by Thiersch[27] in Germany and Duplay[28] in France. Unfortunately, the limited facilities at that time diverted surgeons toward other less successful options.

The main difficulty in this surgery is the replacement of the missing urethra (urethroplasty), and various materials have been used without great cosmetic or functional success. The use of scrotal (hairy) skin as free grafts led to serious complications, particularly severe strictures, infections, and urethral stones. Multistage procedures were the fashion for most of the 20th century, with quite unsatisfactory results that resulted in very traumatized patients. In the middle of this dark age of hypospadias surgery, Mathieu, in 1932,[29] described a very clever flip-flap procedure to reconstruct distal hypospadias using penile nonhairy skin. His procedure is still in use and remains one of the most reliable techniques.

It was not until the early 1970s that this surgery changed dramatically, mainly with the work of Asopa,[30] Duckett,[31] Snyder,[32] Ransley,[33] and Mollard[34] and their colleagues. Well-vascularized urethroplasties using pedicled preputial grafts, preservation of the urethral plate, and the use of free mucosal grafts were important milestones that considerably simplified the surgical approach to hypospadias. Several other pediatric urologists (i.e., Snodgrass,[35] Perovic and Vukadinovic,[36] Koyanagi and colleagues,[37] and Dessanti and associates[38]) brought about valuable improvements in this surgery. Collaboration with endocrinologists, who can stimulate penile growth and healing performances before surgery, also helped greatly in the outcomes of these procedures.

Plastic surgeons, who remain involved in hypospadias surgery in some countries, resurrected two-stage procedures using skin grafts in the latter part of the 20th century (Cloutier,[39] Bracka[40]). Although these procedures may have a

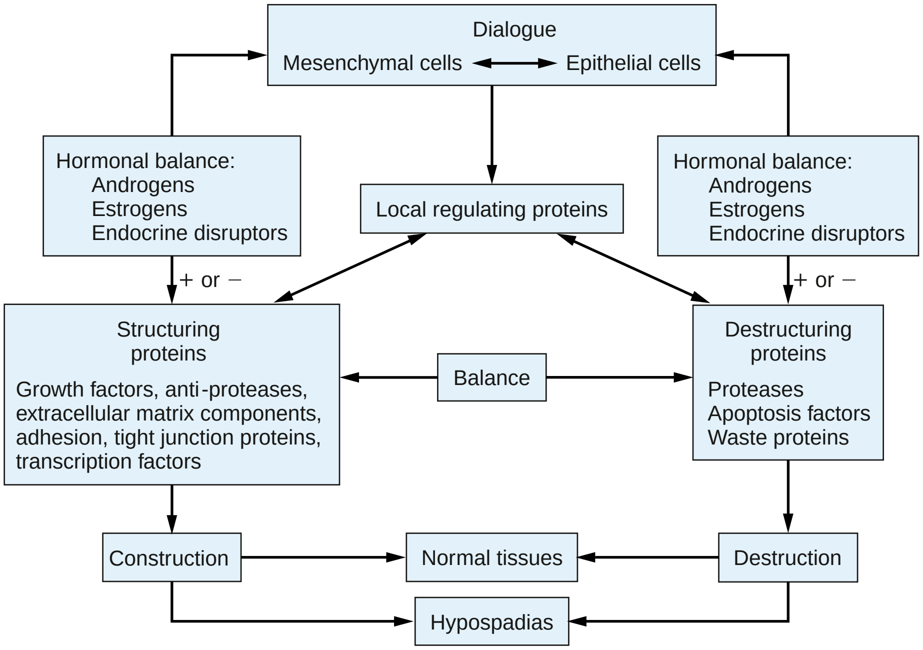
Dialogue
Mesenchymal cells
Epithelial cells
Hormonal balance:
Androgens
Estrogens
Endocrine disruptors
Local regulating proteins
Hormonal balance:
Androgens
Estrogens
Endocrine disruptors
+ or −
+ or −
Structuring proteins
Growth factors, anti-proteases, extracellular matrix components, adhesion, tight junction proteins, transcription factors
Balance
Destructuring proteins
Proteases
Apoptosis factors
Waste proteins
Construction
Normal tissues
Destruction
Hypospadias

Figure 41-9 The balance between structuring and destructuring proteins.

higher risk of urethral stricture, they are perfectly valid for the most severe forms of hypospadias. The use of buccal mucosa instead of skin may improve their results.

SURGICAL PRINCIPLES

In general, hypospadias surgery involves three main steps: (1) straightening of the penis (i.e., correction of chordee); (2) reconstruction of the missing urethra (i.e., urethroplasty); and (3) reconstruction of the tissues forming the ventral radius of the penis (i.e., glans, corpus spongiosum, and skin).

Correction of Chordee

Degloving of the penile skin and freeing of the ventral tissues sitting on each side of the urethral plate usually sorts out the penile chordee related to tethering of the ventral skin and the two spongiosal pillars. If the chordee persists after this first maneuver, freeing of the urethral plate from the ventral surface of the corpora cavernosa, from the glans cap down to the normal urethra surrounded by normal spongiosum, is an alternative advocated by some (Fig. 41-10). In fewer than 5% of cases, the chordee still persists after these two procedures, and a dorsal plication of the corpora cavernosa is then needed.[41] Some authors do not like to free the urethral plate, arguing that this step may jeopardize its blood supply. They prefer to perform a dorsal corporeal plication straightaway. In the most severe form of hypospadias, when a Koyanagi procedure is chosen, the urethral plate is divided behind the glans and detached down to the base of the penis.[37] This complete detachment of urethral tissues from the ventral aspect of the corpora is usually sufficient to straighten the penis, although the procedure is used only for the most severe forms of hypospadias.

Urethroplasty

The choice of urethroplasty depends on the quality and width of the urethral plate (the strip of urethral mucosa extending from the ectopic urethral meatus up to the glans cap).[33] If the urethral plate is wide enough and healthy, it can be rolled to create a urethral tube (Thiersch-Duplay procedure) (Fig. 41-11).[27,28] If the urethral plate is narrow but healthy, various options exist. The most popular one currently is the Snodgrass procedure, in which the urethral plate is incised longitudinally from the ectopic meatus up to the glans. Alternatively, a rectangle of tissue can be isolated and applied onto the urethral plate and stitched to its edges (onlay urethroplasty) (Fig. 41-12).[32,34,36] This rectangle of tissue can be a rectangle of penile skin attached to the ventral edge of the ectopic urethral meatus (Mathieu flip-flap procedure) (Fig. 41-13),[29] or it can be a pedicled rectangle of preputial mucosa (onlay island flap procedure), or it can be a free graft of tissue, usually buccal mucosa (Figs. 41-14)[38] or, less frequently, bladder mucosa[42] or skin.[43]

In rare cases, the urethral plate is not preservable, and a full substitution of the missing urethra has to be performed using a tube of pedicled preputial mucosa (Asopa-Duckett procedure)[30,31] (Fig. 41-15) or a tube of buccal mucosa or the Koyanagi procedure (Fig. 41-16).

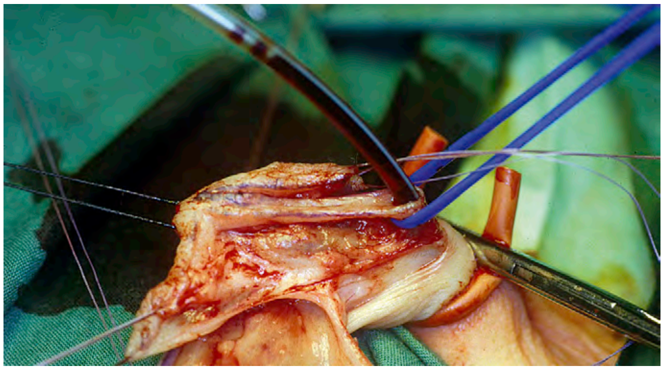

Figure 41-10 Freeing of the urethral plate to release the chordee. The plate remains attached distally to the glans cap and is continued proximally by the urethra.

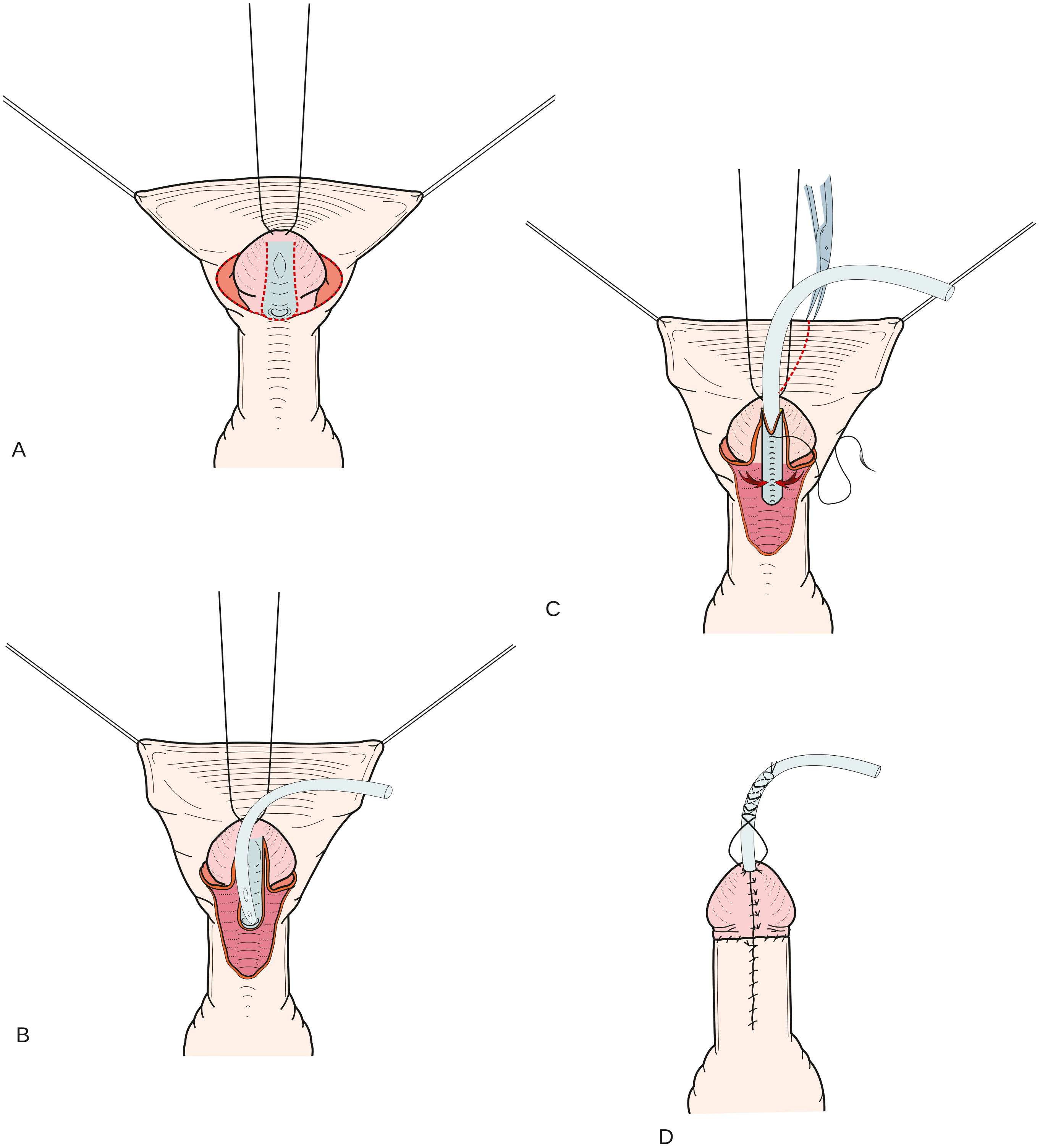

Figure 41-11 The Thiersch-Duplay procedure. **A,** Incision lines. **B** and **C,** Incisions are made along each edge of the urethral plate. The urethral plate is tubularized around an 8F (2.64-mm) to 10F (3.30-mm) catheter. **D,** A Firlit collar, glans plasty, circumcision, and skin cover are performed.

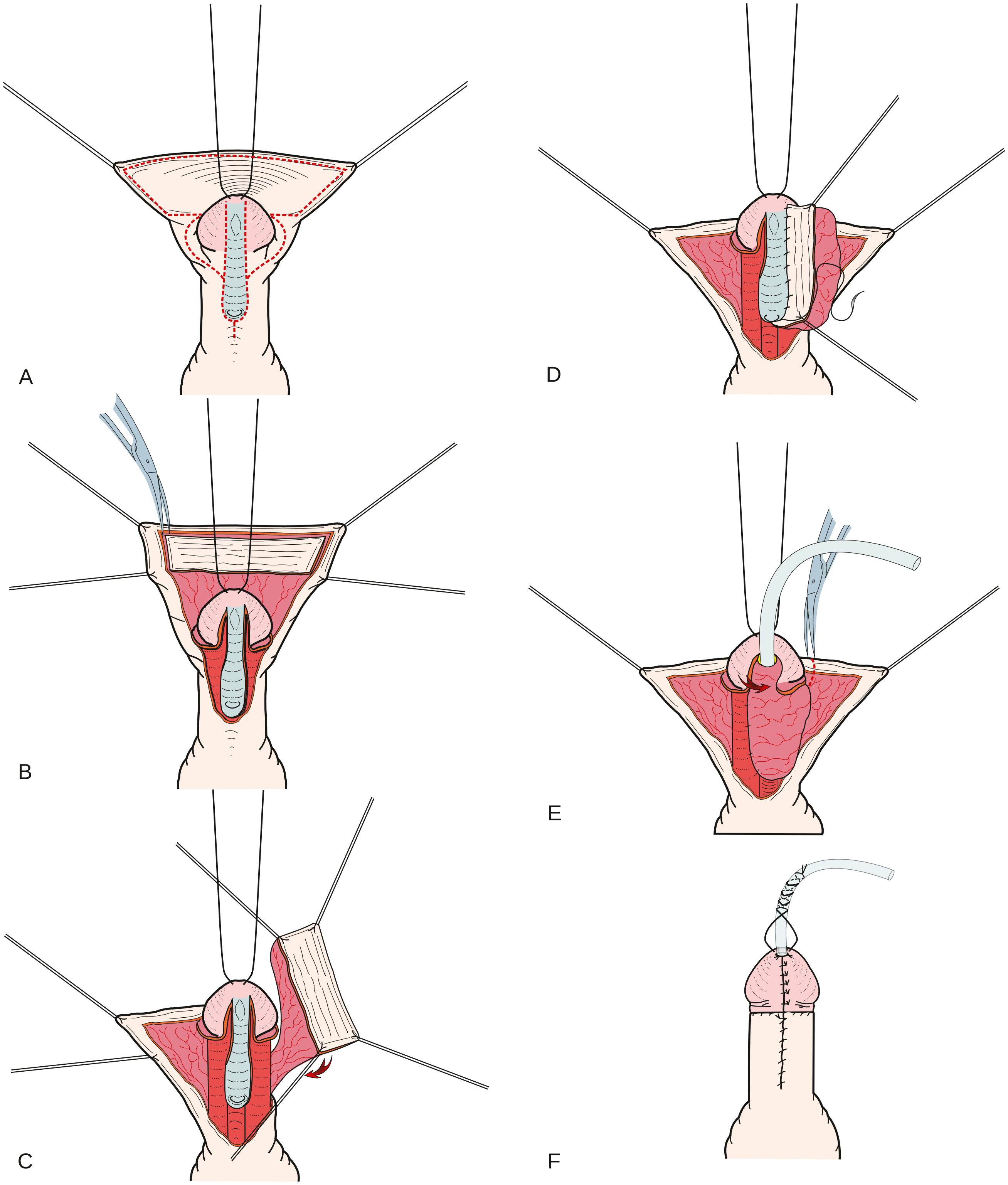

Figure 41-12 The onlay procedure. **A,** Incision lines. **B,** Dissection of a rectangular preputial flap. **C** and **D,** The rectangle of preputial mucosa is positioned as an onlay on the urethral plate, avoiding circular anastomosis. **E** and **F,** The pedicle is mobilized to cover the suture lines. A Firlit collar, glans plasty, circumcision, and skin cover are performed.

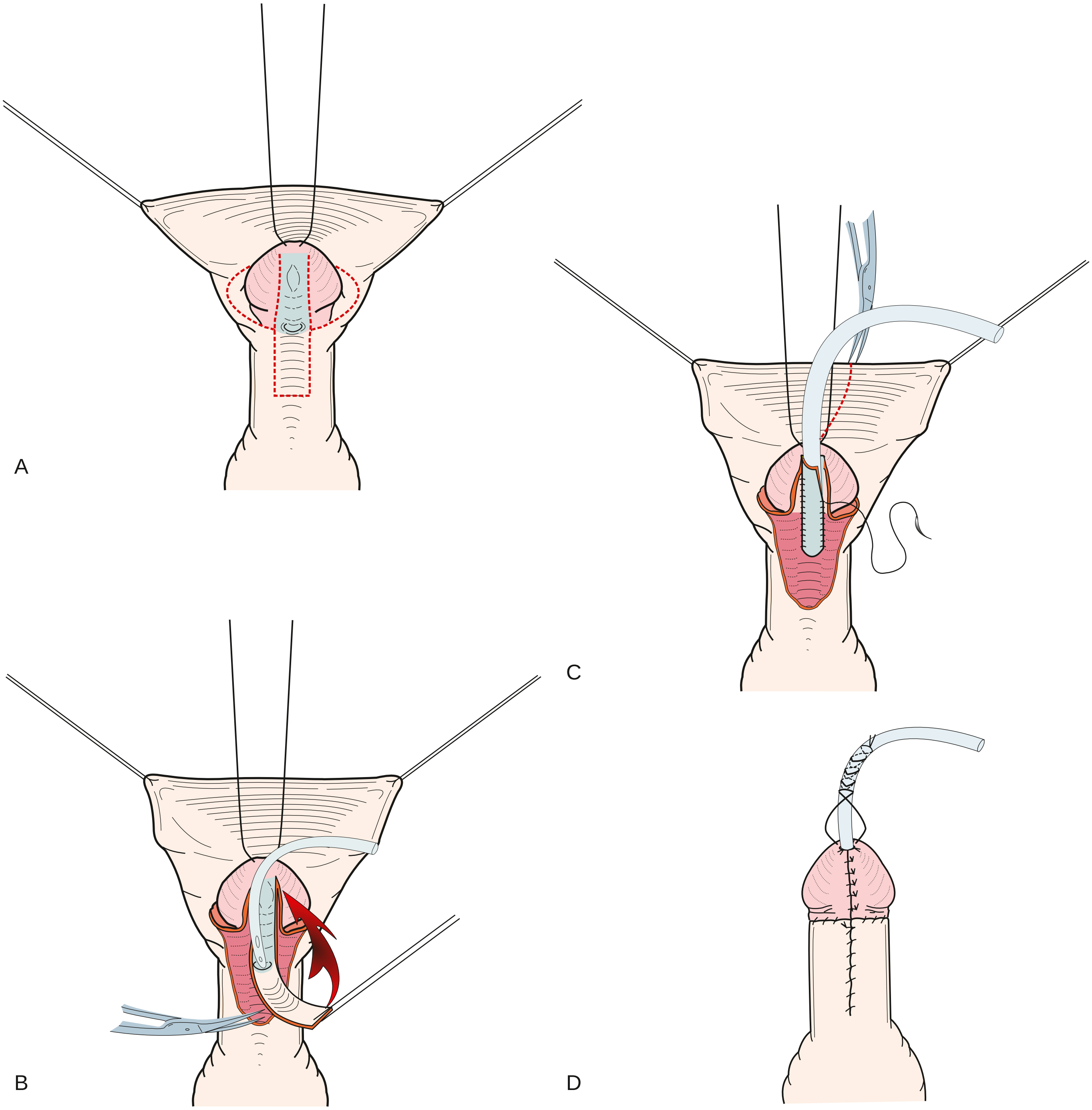

Figure 41-13 The Mathieu procedure. **A,** Incision lines. **B,** Dissection of the Mathieu flap and incision along each edge of the urethral plate. **C,** Suture of the Mathieu flap along the edges of the urethral plate over an 8F (2.64-mm) to 10F (3.30-mm) catheter. **D,** A Firlit collar, glans plasty, circumcision, and skin cover are performed.

In addition to these standard procedures, some other surgical techniques have been described, such as the glans-reshaping procedures for very distal hypospadias, known as the meatal advancement and glanuloplasty incorporated (MAGPI) procedure,[44] which is less popular nowadays; the full mobilization of the penile urethra[45]; and the Turner-Warwick procedures,[46] which have the great advantage of not using any nonurethral tissues to create a full urethra.

Penile Covering

Once the penis is straight and the urethra has been fully reconstructed, many would advocate covering the neourethra with some healthy tissue, such as the two pillars of spongiosum sitting laterally (spongioplasty) or some cellular tissue taken from the dorsum of the penis or the scrotal region. The next steps are the reconstruction of the new meatus (meatoplasty), the creation of a ventral glans (glanuloplasty),

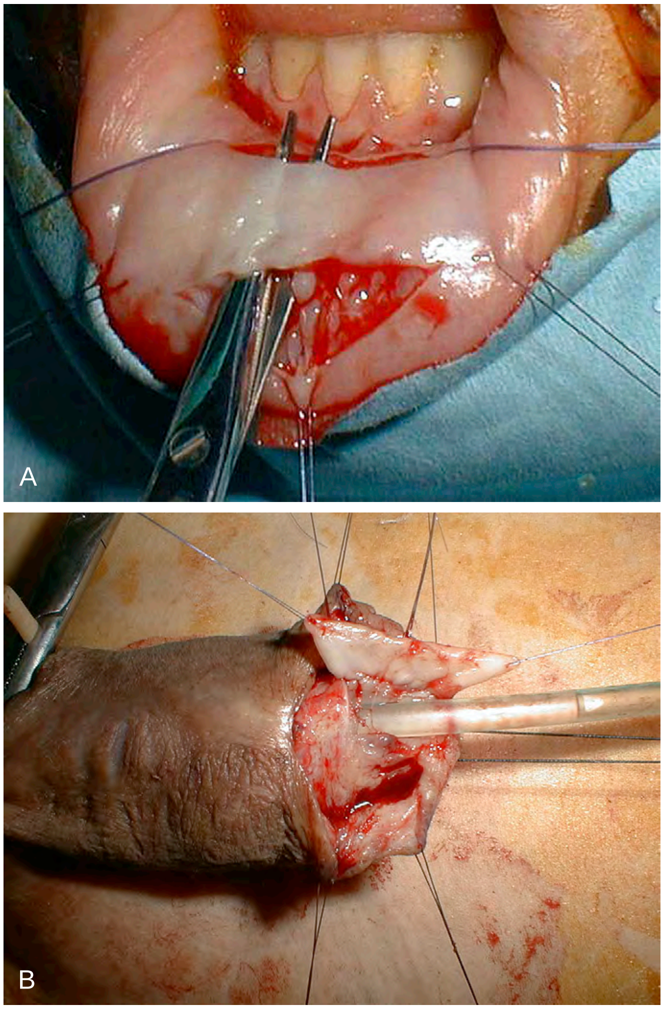

Figure 41-14 **A,** A rectangle of buccal mucosa is harvested from inner aspect of the lower lip. **B,** Buccal graft urethroplasty.

formation of a mucosal collar around the glans (Firlit procedure) (Fig. 41-17),[47,48] and, finally, the skin cover with or without preservation of the foreskin.

CURRENT TECHNIQUES COMMONLY USED BY PEDIATRIC UROLOGISTS

Glanular Hypospadias

These so-called minor hypospadias cases are actually difficult to repair because the distal urethra is often hypoplastic (i.e., not surrounded by corpus spongiosum) and because one can be tempted to favor a minimal procedure as the anomaly appears to be minor. This is the why the MAGPI procedure described by Duckett[44] was, for years, the most popular technique: It is simple to perform and easy to learn. However, the MAGPI procedure has not proved to give long-term satisfactory results in many cases, and more elaborate reconstructions of the distal urethra and ventral glans are used nowadays. A glans ventral tilt or a distal chordee, or both, are commonly associated with these types of hypospadias and are often corrected after degloving of the penis and dissection of the urethral plate.

Procedures Using the Urethral Plate

Rolling the glanular urethral plate (Thiersch-Duplay procedure)[27,28] and covering the reconstructed urethra by means of the two glans wings is a possibility if the glans groove is deep enough. The urethral plate is freed with two vertical incisions following its edges. The two glans wings are deeply dissected laterally. The urethral plate is then rolled around a urethral catheter using fine resorbable sutures (6-0 to 7-0 polydioxanone or polyglactin).

The Snodgrass[35] procedure is an alternative if the distal urethral plate is too narrow to be rolled. A longitudinal midline incision is made on the urethral plate, which is then rolled around a urethral catheter, leaving a raw area inside the urethra, which one hopes is subsequently epithelialized. Snodgrass showed that this procedure was potentially applicable in all cases of primary distal hypospadias, regardless of urethral plate configuration or width.[49] The results are good with a fistula rate of 2% and a glans dehiscence rate of 3%. A general review of literature reported a 9% rate of complications, including meatal stenosis (3%), fistula (5%), partial glans dehiscence (9%), and stricture (2%).[50]

Koff Procedure

A complete mobilization of the penile urethra (Koff procedure[45]) is another possibility to position the urethral meatus at the right place, although this procedure may look quite extensive to some. The whole penile urethra is detached from the anterior aspect of the corpora cavernosa and then moved forward to bring its opening at the tip of the glans. A gain in urethral length of 5 to 15 mm is possible with this technique. More length can be obtained if a more proximal freeing of the urethra is achieved using the Turner-Warwick procedure,[46] although it is rarely needed in these types of hypospadias. The Koff repair has a very low fistula rate, but meatal stenosis appears in about 20% of cases, probably because of a distal ischemia.[51]

These three procedures are attractive because they do not use any nonurethral tissues to repair the missing urethra. Many variations of these procedures have been described, such as the glans approximation procedure[52] or the granular reconstruction and preputioplasty procedure.[53] Barcat[54] described a reconstruction of the distal urethra using one cutaneous flap and one glanular flap.

Mathieu Procedure

In the Mathieu[29] procedure (see Fig. 41-13), two parallel incisions are made on either side of the urethral plate, up to the tip of the glans and deep down to the corpora cavernosa. The incision line delimits a perimeatal-based skin flap that is folded over and sutured to the edges of the urethral plate. The lateral wings of the glans are generously dissected from the corpora cavernosa. The rest of the procedure follows the recommendations given earlier.

Distal strictures are rare (1%), and fistulas are met in 4% of the cases[55] (0.5% meatal retraction and 1% urethrocutaneous fistulas).[56]

The half-moon–shaped meatus is sometimes disappointing, but an extensive dissection of the two wings of the glans allows a nice glanuloplasty. The overall results remain satisfactory.

Meatal Advancement and Glanuloplasty Incorporated

The MAGPI procedure (see Fig. 41-15) involves not an advancement of the meatus but a reshaping of the glans, giving the illusion that the urethral meatus has been moved to the tip of the penis.[44]

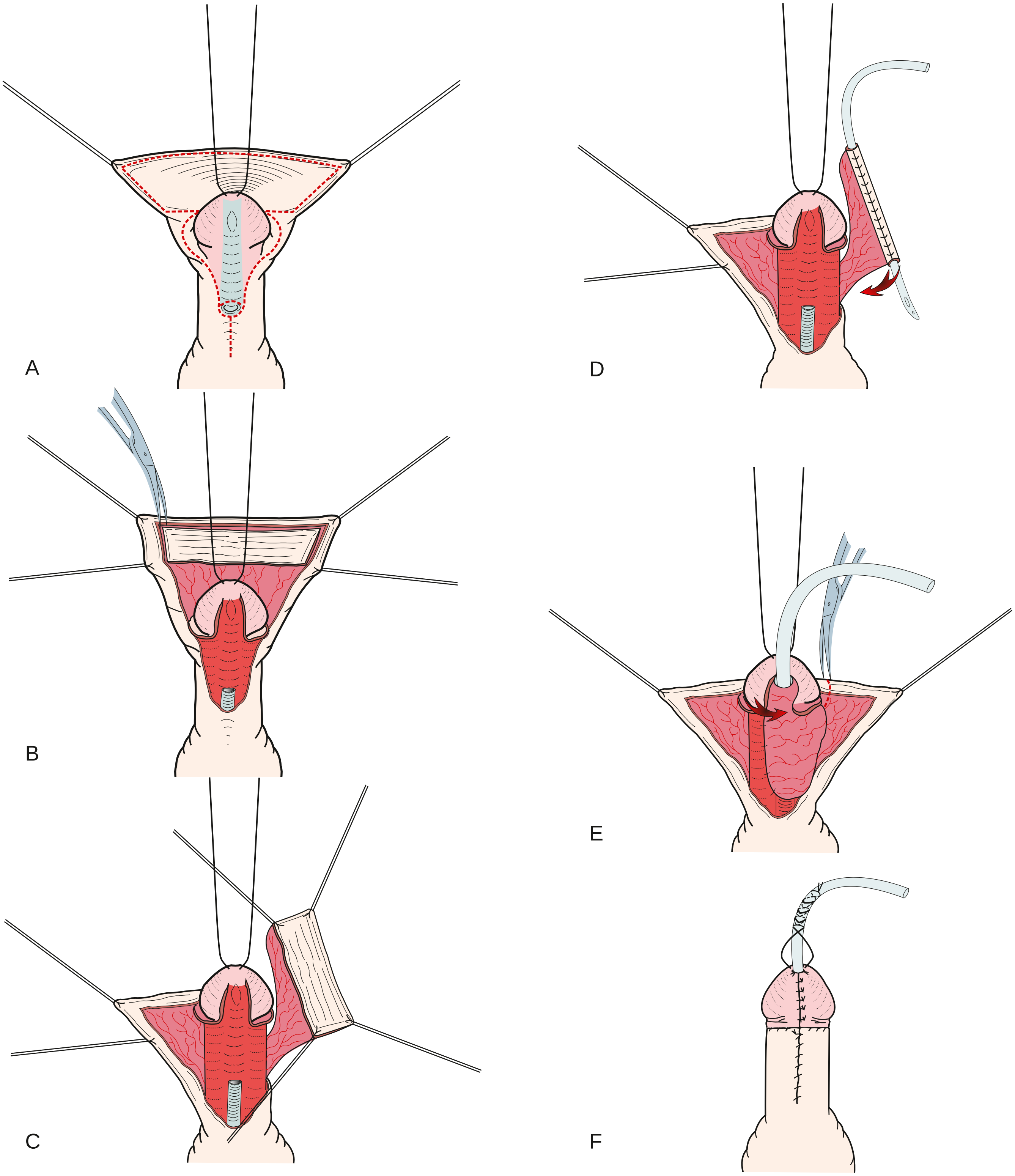

Figure 41-15 The Asopa-Duckett procedure. **A,** Incision lines. **B** and **C,** Dissection of a rectangle of preputial mucosa with its pedicle. **D,** The flap is tubularized around an 8F (2.64-mm) to 10F (3.30-mm) catheter, and a proximal circular anastomosis with the native urethra is performed. **E** and **F,** The pedicle covers the suture lines. A Firlit collar, glans plasty, circumcision, and skin cover are performed.

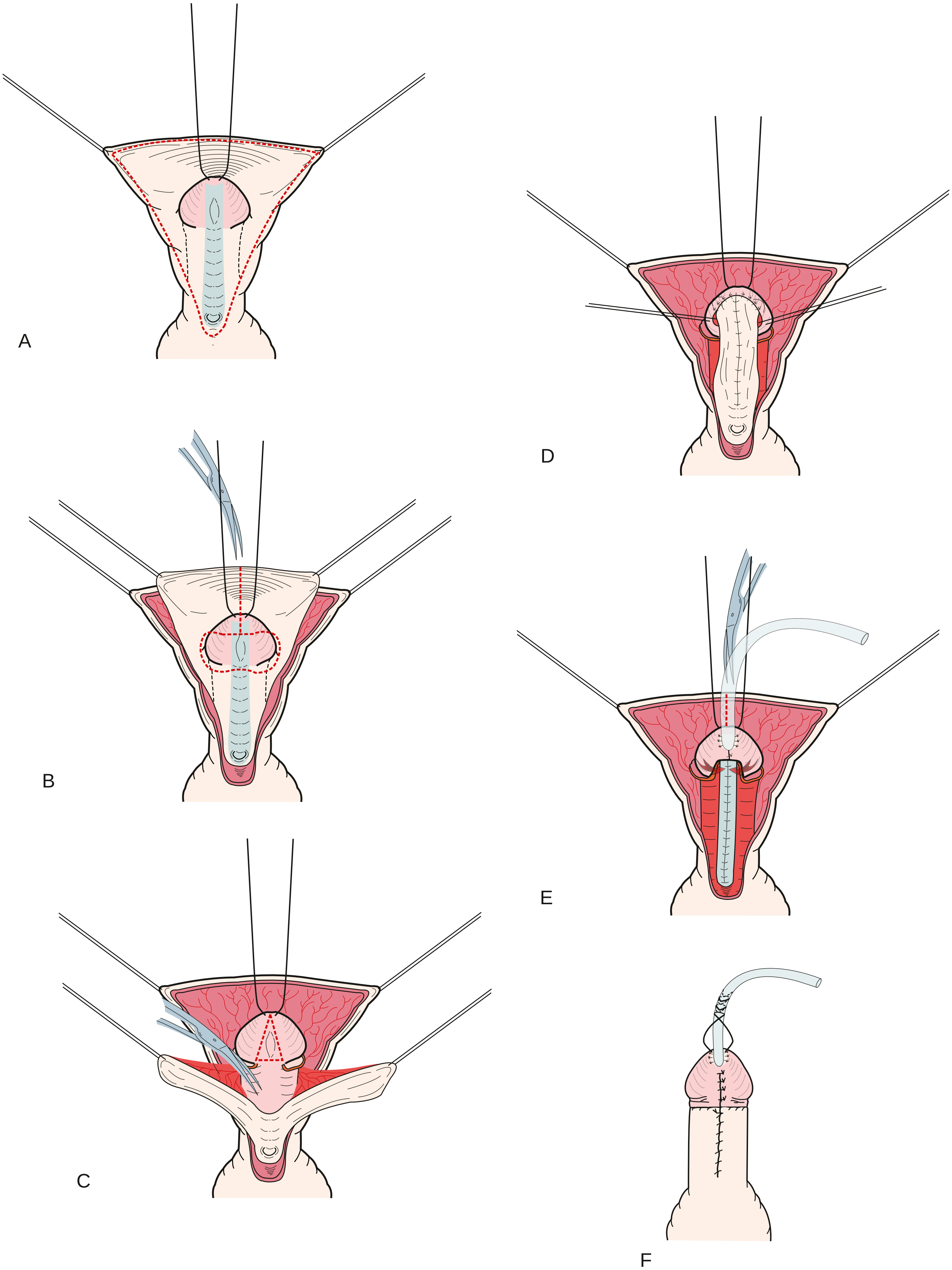

Figure 41-16 The Koyanagi procedure. **A** and **B,** Incision lines. **C,** The preputial mucosa is incised at the 12-o'clock position to form a Y-shaped flap. **D,** The medial edges of the two preputial flaps are sewn together to form the back wall of the neourethra. **E,** The neourethral plate is tubularized around an 8F (2.64-mm) to 10F (3.30-mm) catheter. **F,** A Firlit collar, glans plasty, circumcision, and skin cover are performed.

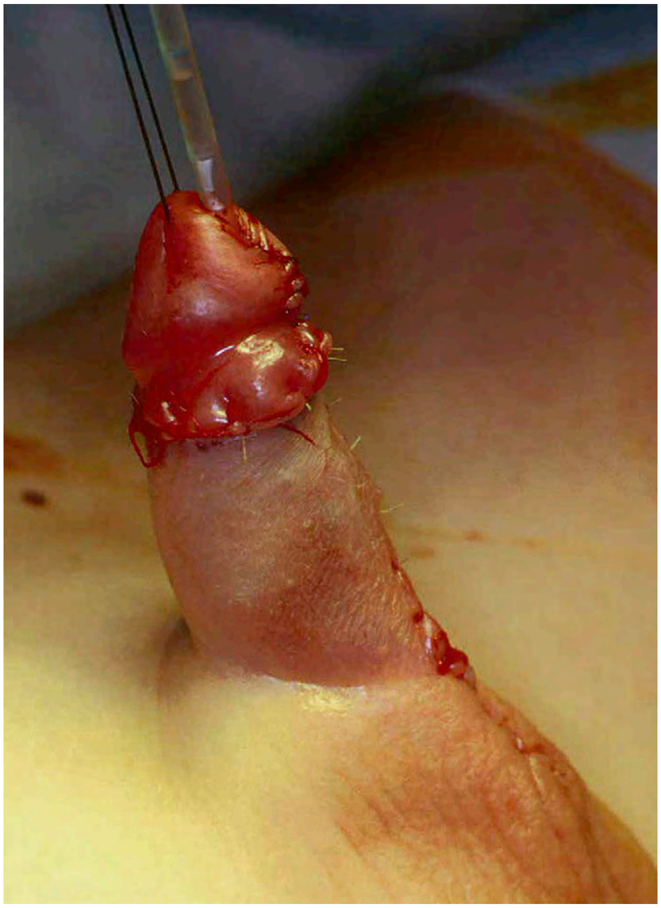

Figure 41-17 End results. Note the mucosal (Firlit) collar surrounding the glans.

The incision line is drawn 5 mm behind the ectopic meatus and following the cutaneomucosal junction of the prepuce. A deep vertical incision into the glanular groove for a distance of about 1 cm opens the dorsal meatus generously. Transverse closure of the diamond-shaped defect that is created flattens out the glanular groove and allows a straight stream to emerge. The ventral lip of the urethra is fixed with a holding stitch and brought forward. This allows the lateral wings of the glans to rotate to the ventrum. A sleeve approximation of the penile skin is done, excising all redundant tissue and leaving a circumcised appearance. It seems that the MAGPI procedure is particularly well indicated when the glans is broad and flat.

In 1992, Duckett and Snyder reported[57] having performed 1000 MAGPI procedures, with 1.2% of their patients requiring secondary procedures. The problems encountered were fistulae (0.5%), meatal retraction (0.6%), and persistent chordee (0.1%). Partial ventral regression of the meatus is a possible long-term complication of this procedure.[58-60] The majority of the complications occurred in the patients with a coronal or subcoronal hypospadias.[61]

Using similar techniques, authors such as Arap and coworkers[62] have slightly modified the MAGPI procedure to improve the cosmetic appearance. The Arap repair advances two flaps of lateral coronal tissue distally, approximating them in the midline, which effectively lengthens the urethra. The glans is then closed over this tissue, normalizing its ventral appearance.

Hypospadias with a Distal Division of the Corpus Spongiosum

In cases of hypospadias with a distal division of the corpus spongiosum and little or no chordee, most current procedures favor the use of the mucosal urethral plate (Thiersch-Duplay[27,28] [see Fig. 41-11]; Snodgrass[35] [see Fig. 41-16]) or a total mobilization of the penile urethra (Koff and associates[45]). The Mathieu[29] procedure (see Fig. 41-13) probably has its best indications for these types of hypospadias. Onlay urethroplasties[32] (see Fig. 41-12) using pedicled preputial mucosa can also be used if the urethroplasty requires more length or more width.

Hypospadias with a Proximal Division of the Corpus Spongiosum

Cases of so-called major or severe or posterior hypospadias (i.e., proximal division of the corpus spongiosum with chordee) require, first, a correction of the chordee, following the steps described earlier: (1) degloving of the penile skin down to its base; (2) for some, freeing of the urethral plate and the distal hypoplastic urethra until sound urethra is found surrounded by the normal corpus spongiosum; (3) freeing of the two lateral vascular pillars of hypoplastic spongiosum; (4) if needed, a dorsal plication of the tunica albuginea of the corpus cavernosum using a Nesbit-type procedure (Fig. 41-18) or similar procedures.[41] After the chordee is fully corrected and checked by an artificial erection test,[63] the urethroplasty is then performed. Extra tissue is often needed to reconstruct the missing urethra.

The first choice for many is a pedicled flap of preputial mucosa that is harvested on the dorsal aspect of the penis and transferred to its ventral side. Onlay urethroplasties avoiding circular urethral anastomosis are favored nowadays, because secondary strictures are far less common with these types of reconstruction. The urethral plate is used as a mooring plate and constitutes the roof of the neourethra. The rectangle of preputial mucosa is stitched along the edges of the urethral plate, using fine resorbable sutures (6-0 to 7-0 polydioxanone or polyglactin). In a review of 5 years' experience at the Children's Hospital of Philadelphia, the onlay island-flap technique had a 5% to 10% fistula rate.[64] Other complications included urethral diverticulum in 0.5%, epithelial inclusion cyst in 0.5%, and meatal stenosis in 1%. Elbakry found a 42% complication rate, including breakdowns in 7%, fistulas in 23%, urethral strictures in 9%, and urethral diverticula in 4%.[65] A recent review of the long-term outcome of 133 onlay urethroplasties[66] used in severe hypospadias showed an overall complication rate of 28.6%, which is quite remarkable compared to other techniques. Tissues sitting on the dorsum of the penis may have a better protein balance than those forming the ventral hypoplastic aspect as shown by the work of Morera and colleagues.[67]

The transverse preputial island flap technique[31] can also be used for this type of hypospadias. This technique ignores the urethral plate, which is excised, and uses a tubularized pedicle flap of foreskin that is interposed between the ectopic meatus and the glans. Because there is a circular anastomosis, the risk of stricture is higher here than in the onlay procedures. The complication rate varies between 3.7%[68] and 69%.[69] Duckett[70] reported a complication rate varying between 9% and 15%. In our series of 84 patients published in 1995,[71] 15% of the patients had fistulas, among which 6% required a secondary procedure. The fistula rate reached 20% in redo procedures. No stricture was recorded. Mollard and Castagnola[72] reported 92 cases of hypospadias with chordee treated by an onlay urethroplasty without division of the urethral plate, including 19 complications in 15 patients (14 fistulas; 3 meatal retractions, and 2 urethroceles). Dewan and colleagues[73] reported an

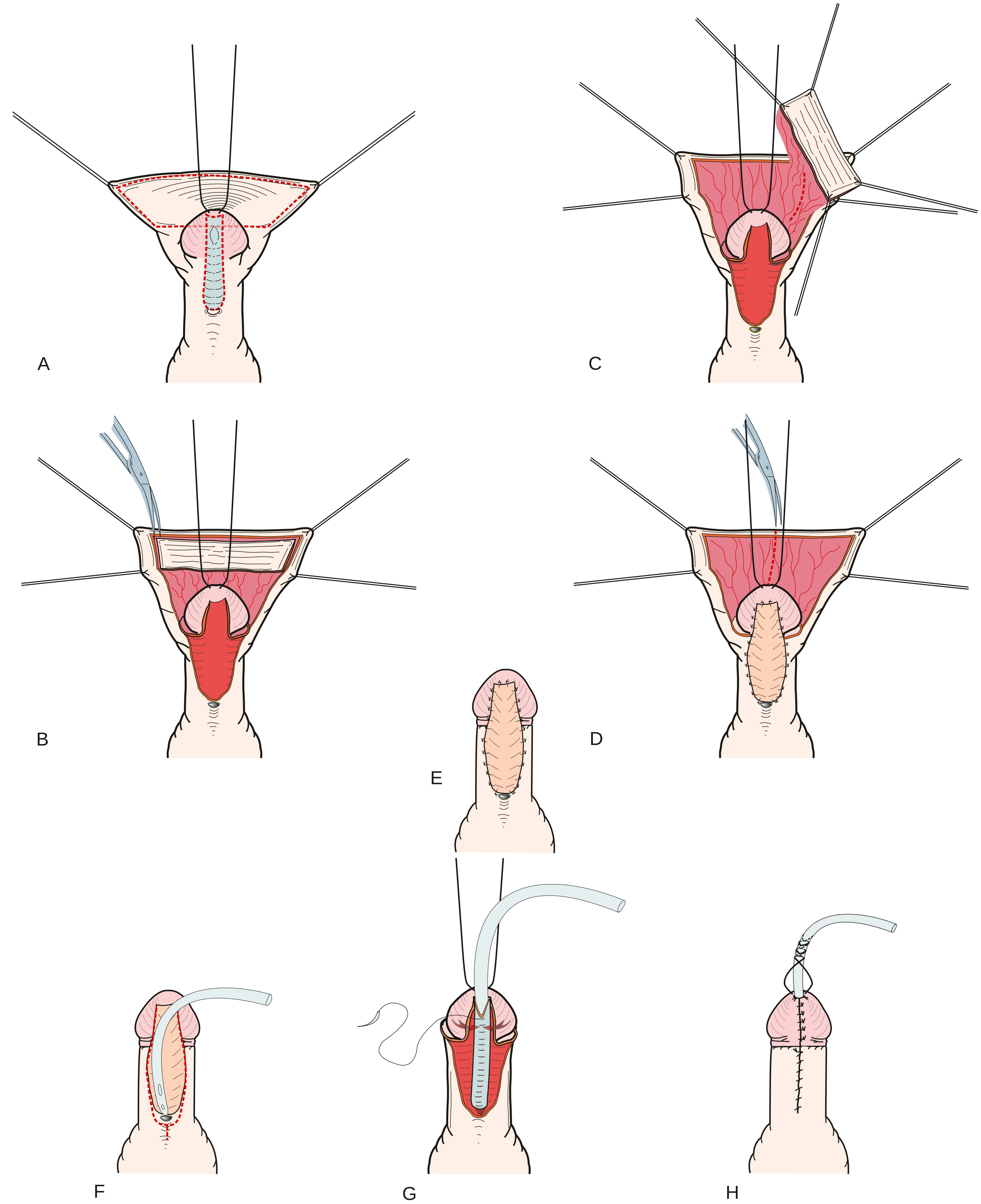

Figure 41-18 The Bracka procedure. Stage 1: **A,** incision lines; **B,** removal of the urethral plate and dissection of a rectangular preputial flap; **C,** positioning of the rectangle of preputial mucosa as an onlay on the ventral aspect of the penis; **D** and **E,** suturing of the graft to the penile shaft, with circumcision and skin cover. Stage 2: **F,** incision lines; **G** and **H,** urethroplasty using the preputial graft and skin cover.

11-year experience with the tubularized preputial flap; fistulas occurred in 34%, urethral strictures in 12%, and meatal stenoses in 18%, with an overall reoperation rate of 50%.

The Snodgrass procedure, also called tubularized incised-plate (TIP) urethroplasty, has been applied to proximal hypospadias in the absence of severe penile curvature and if the incised urethral plate has a supple appearance.[74] The rate of complications was significantly higher at 33%, including fistulas in 21%. Samuel and Wilcox[75] confirmed that adapting the TIP urethroplasty for proximal repair did not drastically increase the incidence of urethrocutaneous fistula. They also claimed that the cosmetic result was superior with the TIP technique.

More recently, a new technique with a dorsal inlay graft using inner preputial skin was described ("Snodgraft").[76] In this procedure, the urethral plate is incised longitudinally. A free graft is harvested from the inner prepuce or the buccal site. The graft is defatted and sutured onto the dorsally incised urethral plate. Then, the neourethra is tubularized. In a report of 32 patients with a 21-month mean follow-up period, no patient had stricture or fistula at the inlay graft site.

Alternatives for reconstruction of severe proximal hypospadias include the Koyanagi repair and its modifications.[37,77] The urethral plate and the adjacent tissues are mobilized with the tissues forming the inner aspect of the preputial hood. A long and wide strip of well-vascularized tissue is mobilized with its blood supply down to the base of the penis. The whole graft is transferred to the ventral aspect of the penis and detached from the anterior surface of the corpora cavernosa. The tissues brought ventrally form the prolonged urethral plate, which is then tubularized from the ectopic meatus up to the glans. Koyanagi and colleagues reported a 47% complication rate but good cosmetic and functional results.[37] A variant of the Koyanagi technique has been reported by Hayashi and colleagues,[78] who avoid the midline division of the preputial hood providing a better blood supply to the substitutive urethra. Both techniques were compared with similar outcome and an overall reoperation rate of approximately 60% of cases.[79] Fistulae, urethral dehiscence, stenosis of the glanular urethra, and urethroceles were the most common complications reported with these two techniques.

If the adjacent penile skin is insufficient for a flap urethroplasty, a graft is required. As a free graft, skin had a poor track record as a urethral substitute, especially extra-genital skin.[80] The use of bladder mucosa graft tissue had a period of popularity, both in primary and secondary cases. However, the overall results were disappointing in the long term, with many complications such as meatal stenosis (28% to 44%), urethral prolapse, fistulas, strictures, and graft dehiscence (24%).[81,82] A free graft of buccal mucosa is the next option. The buccal mucosa is usually taken from the inner aspect of the cheek or from the inferior lip. In a recent series, buccal mucosal grafts had a 32% complication rate and a 14% reoperation rate at 5 years of follow-up.[83] The most common complication reported has been urethral stenosis.[83,84] Duckett and associates[85] found a complication rate of 57% in a series of 30 patients with a 5-year follow-up: 5 cases of meatal stenosis, 7 strictures, 2 fistulas, and 1 breakdown. Buccal mucosal urethroplasty is best used as a patch rather than as a tube graft, with a lesser significant risk of stricture.[86]

Hypospadias Cripple

There are no standardized techniques for redo procedures. Chordee needs to be checked again and, if persistent, corrected by the same steps as mentioned earlier. Buccal mucosa (see Fig. 41-14) is commonly used for redo urethroplasties if there is no preputial mucosa left or if the ventral tissues are too scarred.[38,87] In distal breakdowns, a salvage Mathieu[29,88] or Koff[45] procedure is a potential option. A preoperative course of β-hCG or testosterone or dihydrotestosterone cream can be helpful to improve the blood supply of penile tissues. In all cases, the experience of the pediatric urologist is of paramount importance.

The Snodgrass incised plate urethroplasty has been reported to be an option with successful outcome after failed procedures.[89] Previous incision of the urethral plate was not a contraindication in these selected cases in which the plate appeared supple. However, TIP repair should be avoided in repeat hypospadias surgery if the plate has been resected or is obviously scarred.[90]

Buccal graft urethroplasties in redo cases have a complication rate of approximately 30% in our experience,[87] and 20% in the report of Baskin and Duckett.[91] These complications are mainly represented by fistulas and urethral breakdowns of variable length. However, the plate left after urethral breakdown is usually wide enough to allow a subsequent Duplay urethroplasty. In the severe hypospadias cripple, composite urethroplasty can be indicated.

Multistage Procedures

Multistage procedures have their best indications in cases of severe posterior hypospadias in which the urethral plate cannot be preserved. Some plastic surgeons, such as Bracka[40] (see Fig. 41-18), have reported better cosmetic results using two-stage procedures inspired by Cloutier's[39] technique. The main concern raised by these two-stage procedures is the use of skin to repair the urethra. In the last decades of the 20th century, skin appeared to be a poor material to replace the urethral tissue, because it has an unacceptably high rate of urethral strictures. This is the reason why two-stage procedures using buccal mucosa might provide better long-term results.

The stage-one repair includes an axial incision on the glans, which is completed by a ventral dissection; then a full-thickness graft of preputial skin or buccal mucosa is harvested, sutured in place, and immobilized with a "tie-over" pressure dressing. Six months after the first operation, the stage-two repair is the tubularization of the urethral plate. Although graft manipulation requires an appropriate learning curve, this procedure may be a valid alternative for reconstruction, especially for severe and crippling hypospadias.[92] In his personal series (600 operations in 457 children), Bracka reported a 5.7% fistula rate, and strictures were seen in 7%.[93] The author suggested that, if balanitis xerotica obliterans is present in the genital skin, a buccal graft should be used instead. In a recent series of 62 boys who underwent a two-stage procedure, 1 patient developed a hematoma, 3 patients had a partial glans dehiscence, 3 others kept a residual mild curvature, and 3 boys had a meatal stenosis.[94]

COMPLICATIONS

Complications are common and should be treated at least 6 months after the initial procedure, to allow the tissues to heal properly.

Unsatisfactory Cosmetic Result

Unsatisfactory cosmetic results are common and may include irregular suture lines, skin blobs, or redundant ventral skin forming a jabot. If the ventral aspect of the glans is short and there is no mucosal collar around the glans, the cosmetic result is disappointing. The surgeon's and the patient's views on the cosmetic result are often very different.[95]

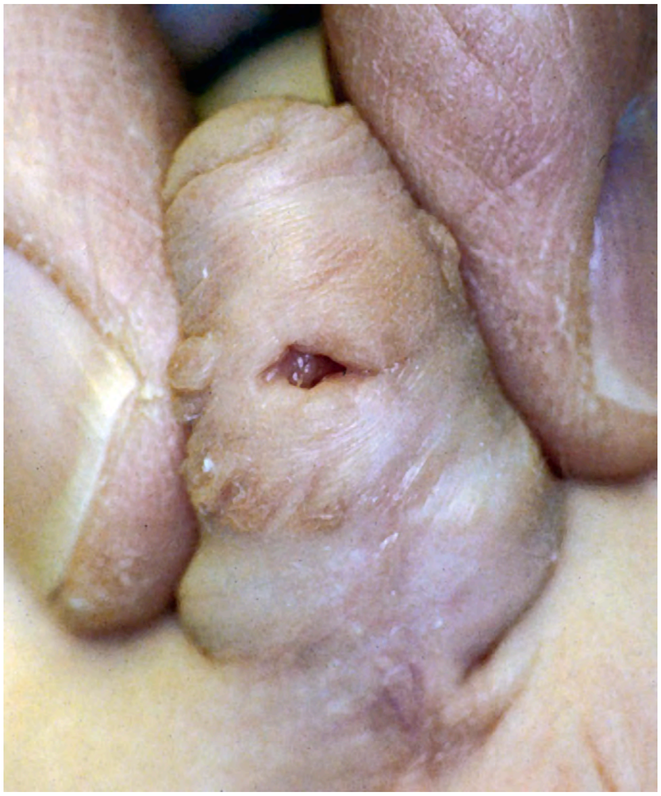

Figure 41-19 Urethral fistula.

Fistulas

Fistulas (Fig. 41-19) are the second most common complication of hypospadias repair. The patient presents with an abnormal stream or drops coming from the undersurface of the penis. Although late fistulas exist, this is usually an early complication (first month postoperatively). A fistula that is small and not associated with a urethral stricture can heal spontaneously. If it persists after 6 months, another procedure is required. The fistula rate varies with the technique used[96]: 4% for the Mathieu procedure but 15% for the onlay procedures in our hands, going up to 20% in cripple hypospadias.[55,71] This complication is more common with free graft urethroplasties than with vascularized grafts.

The location of the fistula varies, but it is often found proximal to the glans corona in a lateral position. If the fistula persists longer than 6 months after the initial procedure, the fistula tract should be excised and sutured and covered by several layers of tissue. Large fistulas are unusual and attest that the original urethroplasty was not satisfactory. They usually require a full reconstruction of the urethra. A combination of fistula and urethral stenosis is common, and therefore the urethroplasty needs to be checked cautiously before deciding on a simple fistula closure. Fistulas located just behind the corona are not easy to close and tend to recur if the usual excision-and-coverage procedure is performed. For this reason, it is often recommended in these cases to redo the distal urethroplasty using a Mathieu flap.

Strictures

Strictures are less common nowadays, because pediatric urologists tend to avoid circular anastomosis and prefer onlay urethroplasties. Meatal stenoses are usually simple to handle by performing a surgical meatal revision. Proximal stenosis is always severe and responds only transiently to urethral dilations, which are unacceptable in children. A redo urethroplasty is often necessary to relieve the obstruction. Ongoing urethral urine flow impairment may lead to abnormal bladder behavior with high-pressure voiding and eventually upper urinary tract damage. It is therefore important to recognize urethral strictures and treat them promptly. However, urine flow studies may not be very reliable to assess the urethral caliber, because they often prove to be abnormal even if the reconstruction is satisfactory.

Mucosal Ectropion

The complication of mucosal ectropion is less common nowadays with the use of onlay urethroplasties. It was commonly observed with bladder mucosal graft urethroplasties[82] and was often associated with pseudopolyps requiring a resection. Recurrence is common, as is secondary meatal stenosis.

Balanitis Xerotica Obliterans

Balanitis xerotica obliterans (BXO) is a rare complication that is related to a chronic inflammation and fibrosis of the meatus and glans. Meatoplasty or redo urethroplasty using buccal mucosa may be required if local application of topical steroids fails.

Urethrocele

Urethrocele is often related to a difference in urethral compliance between the native urethra and the reconstructed urethra. It is therefore important to support the penile urethra with several layers of well-vascularized tissue, to reduce the difference in tissue elasticity. It is also important to check that the urethrocele is not associated with a urethral stenosis. This complication was particularly common with bladder mucosal urethroplasty. Excision of the redundant urethral tissues and treatment of the distal stenosis are required (Fig. 41-20).

Hairy Urethra

Hairy urethra should no longer be seen with modern techniques, although it may reappear with the Koyanagi procedure, because proximal skin is often kept to reform the urethra. This complication is caused by the use of scrotal skin and requires a new urethroplasty. Urethral stones may develop in the hairy segment of the urethra.

Meatal Regression or Glanular Dehiscence

Meatal regression or glanular dehiscence should be avoided through adequate lateral mobilization of glans wings and careful midline approximation of the glans. This complication is commonly seen with the MAGPI procedure. Meatal regression often requires a salvage Mathieu repair.

Persistent Chordee

Persistent chordee is quite rare. The long-term outcomes of plication of the tunica albuginea of the corpora are unknown, and dorsal plication of the corpora at an early age may predispose the patient to secondary penile deformities as the penis grows considerably in the adolescent period. One should therefore be very cautious with these dorsal-shortening procedures, and patients should be followed up through puberty.

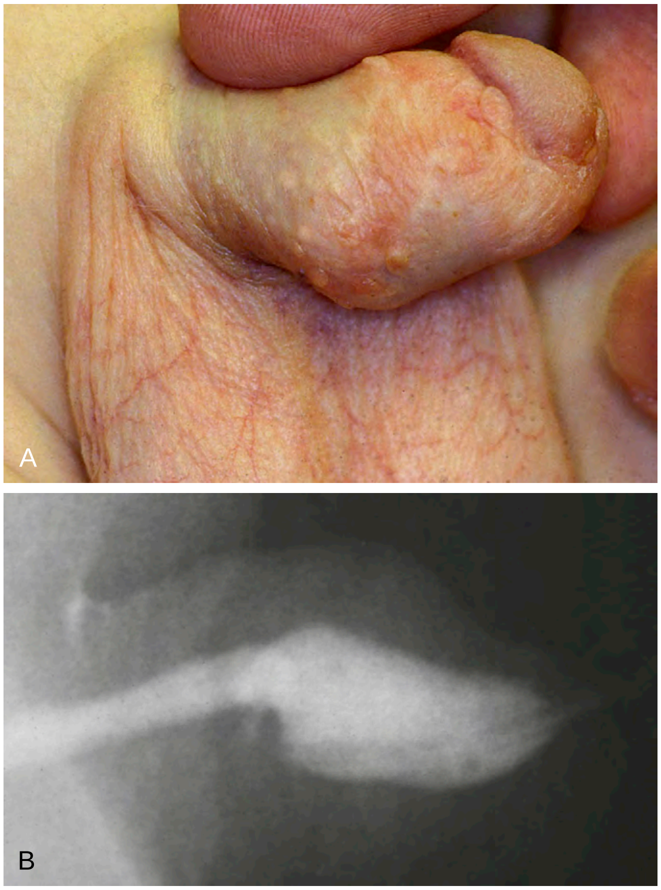

Figure 41-20 **A,** Urethrocele (associated with a meatal stenosis). **B,** Urethrography of the same patient as in **A.**

Disasters: Cripple Hypospadias

Cripple hypospadias situations result when multiple surgical interventions leave behind persistent chordee, fibrous patches, scarred tissues, irregular skin, and multiple fistulas partially covered by skin bridges. Cripple hypospadias is often the result of traumatizing dissection, poorly vascularized tissues, sutures under tension, inappropriate urine drainage, infection, and misdiagnosis (intersex), among other causes.

Long-Term Psychological Implications

The long-term psychological implications of hypospadias repair are very important, but only a few long-term studies have been published.[95,97-99] They mainly showed that the sexual life of hypospadias patients is often normal, although it may start at a later age compared with controls. More hypospadiac patients (33%) than controls (12%) were inhibited in seeking sexual contacts.[95] Erection should be normal, and fertility is not affected unless the hypospadias is associated with undescended testes.

LONG-TERM OUTCOMES

Few publications exist regarding long-term outcomes of modern procedures. The long-term results available today mostly concern procedures that have now been abandoned. The Denis Browne procedure does not provide satisfactory long-term results. In most cases, the meatus remained proximal to the glans at the middle third of the penile shaft,[100-102] and a quarter of these patients had difficulty in urinating while standing. Two thirds had a spraying stream. Bracka[103] reported that half of the patients who underwent a Denis Browne procedure[104] or an Ombredanne procedure[105] needed further surgery. More than 30% of posterior hypospadias patients had complex longstanding problems.[106]

Although early outcome data are widely available, little has been reported on the long-term problems. Data suggest that most men have no lasting effects, but up to 40% of those with severe hypospadias have some degree of voiding problems. Recently, Khoury and coworkers[107] described long-term follow-up of the TIP repair: 69% of patients had normal urinary peak flow rates, and 46 of 48 patients had a postvoid residual of less than 10%. In a study of island tube and island onlay repairs with a mean follow-up period of more than 14 years, Snyder and colleagues[108] found normal urine flow rates in all patients, although this result does not match what other authors have published. Long-term urinary outcomes in patients undergoing a free flap repair were recently reported. In a review of 44 boys who had undergone two-stage repair for severe hypospadias, 40% described urinary spraying, and 40% milked the urethra after voiding.[109] The result was similar in a group of patients after buccal mucosa grafts, with 26% describing problems with urinary spraying.[110]

An objective assessment of the cosmetic appearance after hypospadias is difficult. In a recent objective study, 32 boys had their penis photographed after three different types of repair: TIP, Mathieu, or onlay. The TIP repair was believed to have the most cosmetically appealing result.[111] Lam and colleagues, in their long-term review of two-stage repairs, reported that 92% of patients were pleased with the outcome, and 88% considered their penis to be normal.[109] In contrast, Nelson's group reviewed single-staged buccal urethroplasty for severe cases of hypospadias and found that only 28% were very satisfied with the appearance of the penis.[110]

Concerning sexual outcome, problems affecting erection, ejaculation, and sexual sensation have been reported in more than 20% of men, in several studies.[110,112,113]

TECHNICAL TIPS

Most surgeons use magnification glasses for this surgery. Endless debates exist about the use of antibiotics, coagulation, tourniquets, types of urine drainage, dressings, and sutures. Each surgeon has his or her own habits, and each needs to compare honestly his or her results with others.

Surgical repair can be carried out starting from 6 months of age, and before 2 years if possible. Children younger than 2 years of age have reflex micturitions that facilitate the postoperative period. Among children who have bladder control, first micturitions after surgery might be more difficult to initiate.

Preoperative penile hormonal stimulation is an issue for discussion, and there is no agreement about the dose and type of stimulation that should be used. β-hCG, systemic testosterone administration, local dihydrotestosterone cream, local testosterone cream, epidermal growth factor, and growth hormone are regularly discussed as means to improve the size of the penis and its ability to heal. Little is known about the long-term effects of these hormonal treatments, particularly concerning growth and precocious puberty. Recent publications from dermatologists[114] showed that androgens may slow down the healing process. A publication to come from our department shows that patients who received preoperative androgen stimulation have a significantly higher rate of healing complications (i.e., fistula and dehiscence) than those who did not. This study recommends a period of at least 6 months between the androgen stimulation and the surgical reconstruction.

The current tendency is to keep these children in the hospital for as short a time as possible, to reduce the psychological impact of the surgery. It seems that the best age for this surgery is probably between 12 and 24 months. Here again, there is a lack of data, and opinions may swing like a pendulum.

CONCLUSIONS

Hypospadias surgery remains very challenging, with a significant complication rate even in the best hands. This surgery should be performed by experienced pediatric urologists who handle at least 40 to 50 cases per year per surgeon.

Preoperative and perioperative treatments affecting the healing capacity of the patient are promising fields of research that may improve the outcome of this difficult surgery.[115-120] The unbalanced protein platform that characterizes the ventral aspect of the hypospadiac penis might be modified before surgery to reduce some complications often met with current procedures. The main challenge for this century is to find an adequate tissue to replace the missing urethra (neither skin nor buccal mucosa nor bladder mucosa is entirely satisfactory), and urothelial cell cultures may provide an easy-to-handle material for urethroplasty.[121,122]

REFERENCES

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CHAPTER 42

DISORDERS OF THE PENIS AND SCROTUM

George Chiang and Marc Cendron

Anomalies of the male external genitalia may be confined to overt clinical appearance, or they may provide clues to underlying disorders that require further evaluation. These anomalies can be broadly divided into three categories: (1) congenital abnormalities, (2) anomalies associated with other conditions, and (3) acquired or iatrogenic anomalies. A working knowledge of the embryologic development of the male genitalia is essential to identification and understanding of the etiology of congenital anomalies. Current work on mapping of the human genome has implicated a variety of chromosomes that are integral to gonadal development. Deletions of chromosome 9p and 10q have been associated with primary sex reversal of 46,XY individuals, indicating that these regions harbor genes essential for testicular development.[1] Although most congenital conditions encountered in the clinical setting are benign and do not require extensive evaluations, others require a significant amount of time spent on assessment and planning of their management, because they may have long-term health implications.

DEVELOPMENT OF MALE EXTERNAL GENITALIA

The development of the male genitalia occurs between weeks 9 and 14 of gestation. Current imaging technology allows for the identification of male genitalia and potential abnormalities only at about 18 weeks' gestation. Ultrasound can be an important adjunct in the antenatal diagnosis of urogenital anomalies, and it is not limited by maternal body habitus, oligohydramnios, or fetal position[2] (Fig. 42-1). Magnetic resonance imaging (MRI) has also been used but is still considered a research tool.[3]

The biochemical stimulus for differentiation of the external genitalia in males is testosterone, and its byproduct is dihydrotestosterone. The masculinization process is initiated by human chorionic gonadotropin (hCG), which is produced by the placental syncytium. The hCG causes fetal Leydig cells to release testosterone, which, along with dihydrotestosterone, binds androgen receptors located in epithelial and mesenchymal cells in the area of the external genitalia.[3] The external genitalia are formed by several fetal structures: (1) the genital tubercle, which will become the glans penis; (2) the genital folds, which will differentiate into the penile shaft; and (3) the labioscrotal folds, which will become the scrotum (Fig. 42-2).[4]

The process by which the penis develops occurs rapidly in concert with the elaboration of the urethra, so that by 9 weeks of gestation, a fully formed penis above the scrotum can be identified.[5,6] By 15 weeks, a shift in the endocrine environment occurs: fetal testosterone secretion is maintained by stimulation from luteinizing hormone (LH) produced by the fetal pituitary gland. Throughout the rest of gestation, the penis continues to grow progressively. After birth, a transient surge in testosterone levels during the first 4 months of life causes further penile growth. Genital growth then remains minimal until puberty.

Normal anatomy of the penis includes the foreskin, the glans, the urethral meatus, the penile shaft, and skin coverage with the median raphe on the ventral aspect of the penis. The scrotum is located below the penis and varies greatly in size and appearance.

PENILE ANOMALIES

Congenital penile or scrotal anomalies can be isolated variations of external genitalia development, or they can represent significant underlying malformations. Prompt diagnosis and potential surgical planning are essential to allay the anxieties of parents as well as to identify other, potentially clinically significant conditions. Congenital penile anomalies have been shown to be increasing in incidence. The weighted incidence of anomalies including hypospadias has increased from 7 of every 1000 newborns (1988-1991) to 8.3 of every 1000 newborns (1997-2000),[7] but this may be a result of increased reporting. Multiple etiologies in abnormal development have been proposed, including genetic, hormonal, and environmental influences.[8] Whereas molecular pathology has aided in the identification of key steps in abnormal development, modern imaging techniques continue to refine the evaluation and treatment of such anomalies.

Aphallia

Aphallia (Fig. 42-3) is very rare, with only about 70 cases reported in the medical literature. Its estimated incidence is 1 in 10 million births. This devastating abnormality is thought to result from a failure of the genital tubercle to develop normally.

Classification

Two classification schemes have been proposed. Skoog and Belman[9] based their classification system on the opening of the urethral meatus. In type 1 aphallia, the urethral meatus opens below the urinary sphincter or is postsphincteric. In type 2, it is at the level of the prostatic urethra with a communication to the rectum in the form of a fistulous tract. In type 3, it is at the level of the bladder, with no urethra seen, and a vesicorectal fistula allows for urinary drainage. Evans and colleagues[10] classified aphallia based on the severity of associated anomalies. Patients with severe cases present with renal aplasia or dysplasia and other caudal anomalies. A less severe form is associated with low mortality and few associated anomalies.

Associated Congenital Abnormalities

A high rate of associated congenital anomalies (>50%) is seen with aphallia. Approximately one third of cases are seen in association with stillbirth or neonatal death secondary to bladder outlet obstruction and resulting pulmonary hypoplasia.[9] Aphallia falls into the category of urorectal septum malformations (URSMS). The more proximal the urethral meatus, the higher the mortality rate and the more severe the associated anomalies. The incidence of associated anomalies is lower

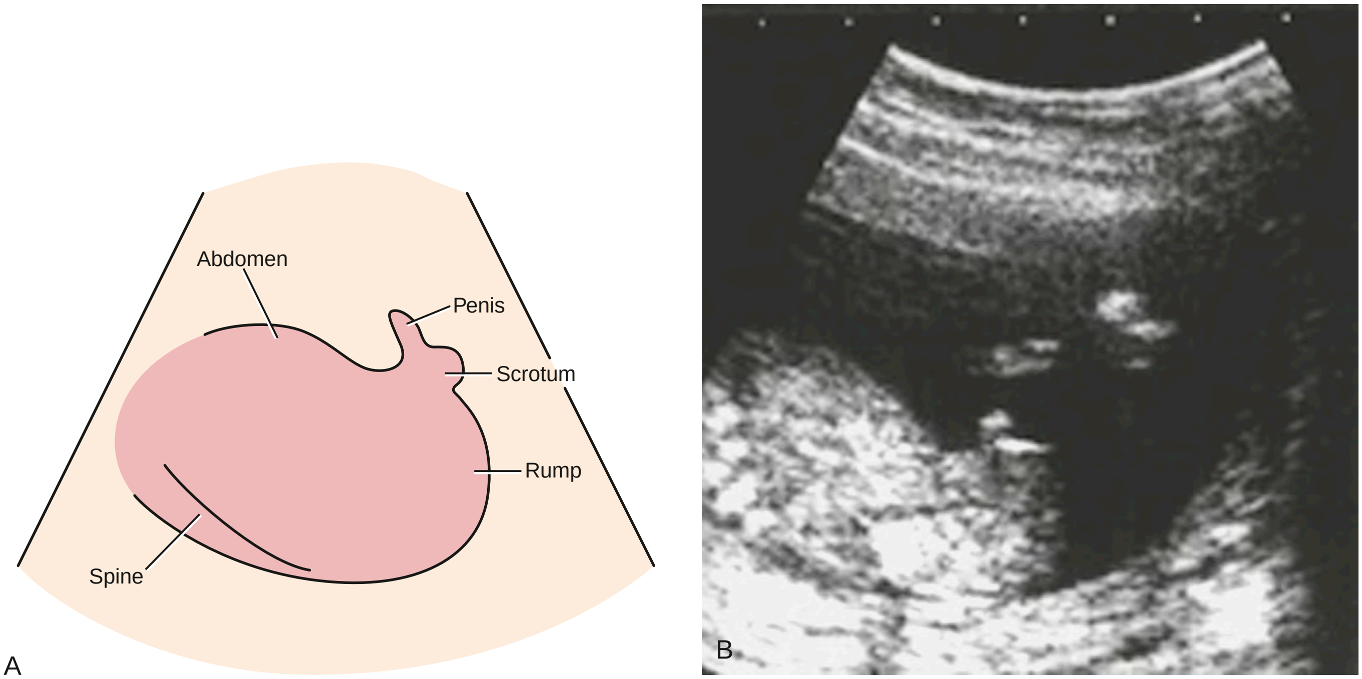

Figure 42-1 Schematic **(A)** and ultrasound **(B)** sagittal views of male genitalia at 18 weeks. Note how the penis points "up" toward the head. (Courtesy of Dr. Douglas S. Richards.)

in patients who have some degree of urethral development. Associated anomalies include testicular maldescent, renal anomalies, vesicoureteral reflux, imperforate anus, and musculoskeletal and pulmonary abnormalities.[10]

Vesicorectal fistula occurs in patients with no urethral development. This is caused by very early bladder outlet obstruction. In these cases, associated anomalies are much more frequent (an average of four per patient), and mortality rate is closer to 100%.

Evaluation

Prenatal diagnosis has not been reported to our knowledge. A karyotype may not be necessary, because invariably these patients are XY. Further evaluation is required to determine the presence of associated anomalies and should be tailored to the physical findings. MRI has been helpful in further defining the lower urinary tract and gastrointestinal tract and in demonstrating the presence of erectile tissues.[11] The presence of erectile bodies may help in planning the reconstructive procedure, but, in general, corporal bodies are absent or severely hypoplastic.

Treatment

Gender reassignment has been recommended in the past, given the formidable obstacles to surgical reconstruction of a functional penis and urethra. However, a recent report questioned the option of gender reassignment because of the early impact of testosterone imprinting on the brain, which leads to significant psychosocial difficulty as the gender-reassigned child matures. In 16 patients assigned to the female gender at birth or reassigned to female during early childhood, 2 lived as males later in adolescence or adult life. In 17 patients raised as males, all continued to live as males.[12]

Prior to this report, the standard of care had been removal of the male gonads and creation of a functional female genital and urinary tract. This approach must be still considered an extensive surgical endeavor. Reconstruction of the urethra may be the most challenging portion of the surgical procedure, because it involves de novo elaboration of a functional bladder neck and urethra. In 1987, Stolar and coworkers described the use of a posterior sagittal approach for reconstruction of the lower urinary tract.[13]

More recently, a one-stage reconstruction has been reported. The reconstruction was accomplished with the creation of a neovagina using a colon segment. To date, vaginal reconstruction using sigmoid colon has shown no long-term complications in regard to patency or comesis.[14] There have also been reports of one-stage correction using an anterior sagittal approach.[15]

The current approach to treating a child born with aphallia includes the following:

1. Careful and expeditious evaluation at a tertiary care center
2. Parental counseling with a discussion of gender reassignment
3. Involvement of a multidisciplinary team including behavioral medicine specialists, endocrinologists, psychologists, urologists, and social workers
4. If gender reassignment is chosen, orchiectomy in a one-stage procedure including genitoplasty, urethroplasty, and, if deemed possible, vaginoplasty using a combined transabdominal and perineal approach. If the parents choose not to have the child gender-reassigned, long-term counseling should still be provided. Early reconstruction of the lower urinary tract and penis should be carried out. Successful phallic reconstruction with radial forearm flaps or fibular flaps in adult life has been reported.[16] Lifelong follow-up by a pediatric urologist is clearly warranted.

Micropenis

Micropenis is unusual but can result from multiple hormonal abnormalities. It constitutes 1.8% of all congenital penile anomalies.[17] True micropenis is unusual and should

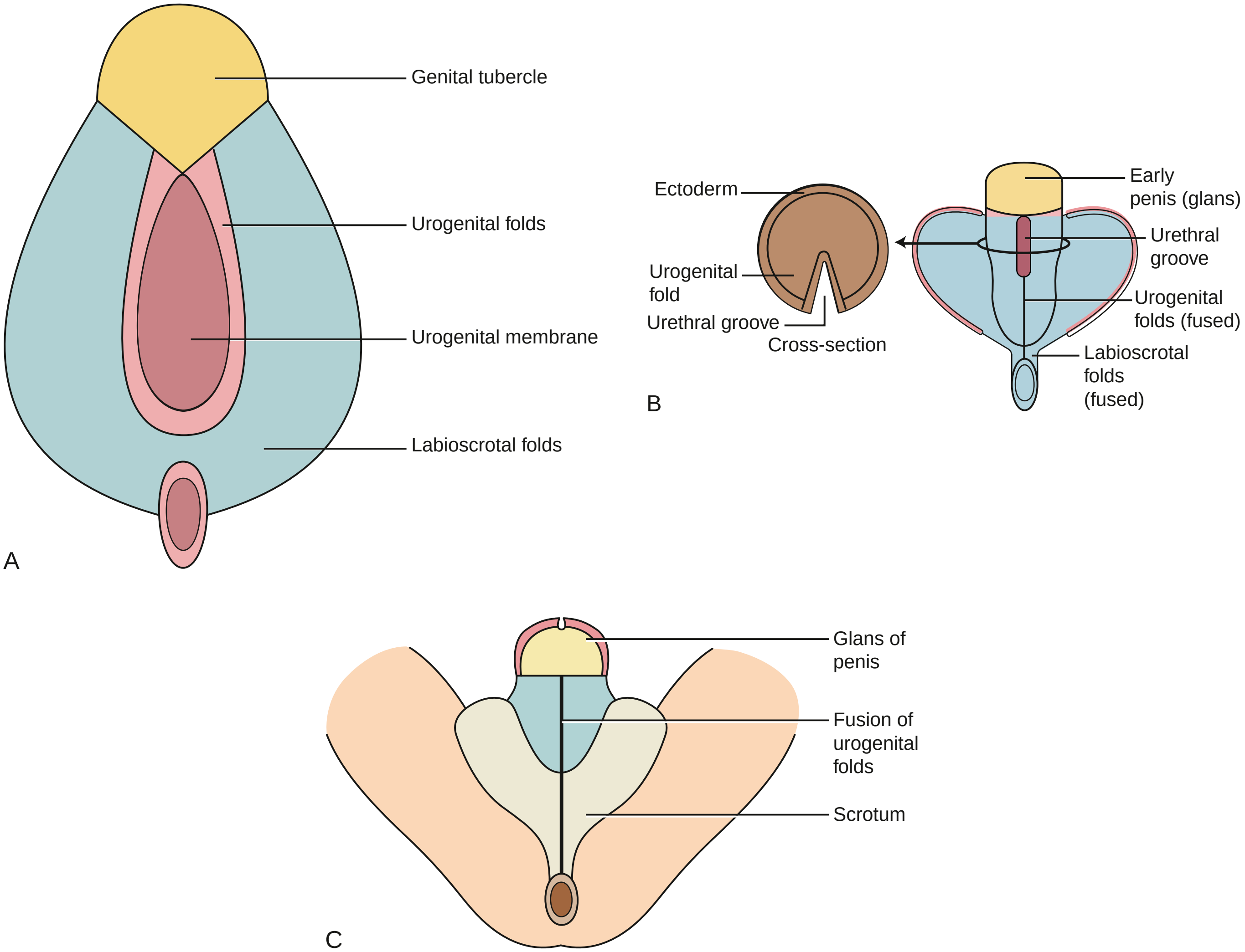
Genital tubercle
Urogenital folds
Urogenital membrane
Labioscrotal folds
A
Ectoderm
Urogenital fold
Urethral groove
Cross-section
Early penis (glans)
Urethral groove
Urogenital folds (fused)
Labioscrotal folds (fused)
B
Glans of penis
Fusion of urogenital folds
Scrotum
C

Figure 42-2 Normal anatomic development. **A,** External genitalia at 7 weeks (undifferentiated). **B,** External genitalia at 9 weeks. **C,** External genitalia at 12 weeks. (Courtesy of Dr. Eugene Daniels.)

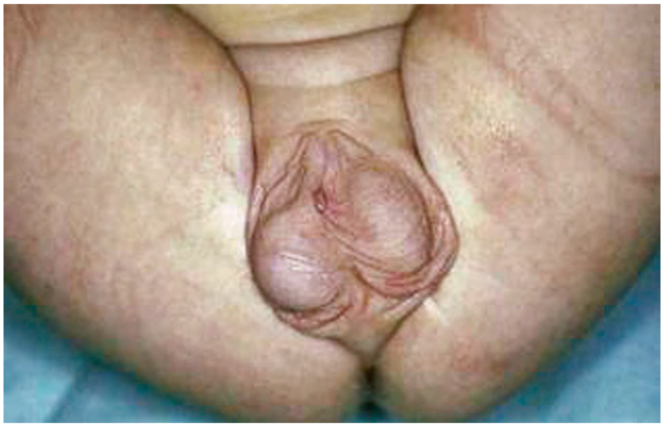

Figure 42-3 Aphallia. (From Perovic S, Djakovic N, Hohenfellner M. [Penile and urethral anomalies]. [German] *Urologe A.* 2004;43:394-401.)

be distinguished from a buried or webbed penis. As discussed earlier, normal penile development requires the appropriate timing and secretion of testosterone from Leydig cells. During the first 3 months of gestation, the process is mediated through placental hCG. In the 4th month, with the penis being fully formed, LH and follicle-stimulating hormone (FSH) stimulate testosterone secretion. This process is driven by gonadotropin-releasing hormone (GnRH), which is produced by the fetal hypothalamus. It follows that micropenis results from failure of the normal stimulation of penile growth after 14 weeks of gestation. Two major causes of abnormal hormonal stimulation have been identified: (1) inadequate secretion of GnRH (hypogonadotropic hypogonadism), which is the most common cause of micropenis, and (2) failure of the testes to produce testosterone[18] (Fig. 42-4 and Table 42-1).

Classification

The strict definition of micropenis is one in which the stretched length of the penis is more than 2.5 standard deviations (SD) below the mean.[19] For a newborn to be classified as having a micropenis, his stretched penile length should be smaller than 1.9 cm. Normal penile size in the term male newborn is 3.5 ± 0.7 cm in the stretched length and 1.2 ± 0.2 cm in diameter. Careful measurement should be taken by gripping the glans firmly and placing a rigid ruler on the dorsal aspect of the penis, from the pubic symphysis to the tip of the glans.

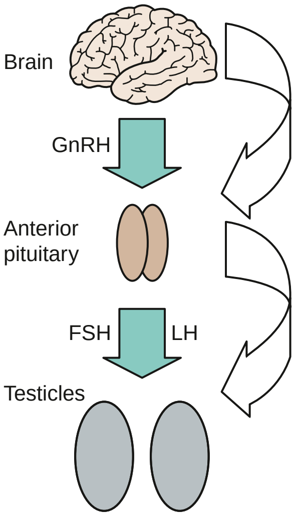

Figure 42-4 Abnormal development leading to micropenis. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

Table 42-1 Causes of Micropenis

Hypogonadotropic Hypogonadism
1. Isolated, including Kallmann's syndrome
2. Associated with other pituitary hormone deficiencies
3. Prader-Willi syndrome
4. Laurence-Moon syndrome
5. Bardet-Biedl syndrome
6. Rud's syndrome
Primary Hypogonadism
1. Anorchia
2. Klinefelter's and poly-X syndromes
3. Gonadal dysgenesis (incomplete form)
4. Luteinizing hormone receptor defects (incomplete forms)
5. Genetic defects in testosterone steroidogenesis (incomplete forms)
6. Noonan syndrome
7. Trisomy 21
8. Robinow syndrome
9. Bardet-Biedl syndrome
10. Laurence-Moon syndrome
Defects in Testosterone Action
1. Growth hormone/insulin-like growth factor I deficiency
2. Androgen receptor defects (incomplete forms)
3. 5α-Reductase deficiency (incomplete forms)
4. Fetal hydantoin syndrome

Adapted from Bin-Abbas B, Conte FA, Grumbach MM, Kaplan SL. Congenital hypogonadotropic hypogonadism and micropenis: effect of testosterone treatment on adult penile size: why sex reversal is not indicated. *J Pediatr.* 1999;134:579-583.

Evaluation

On initial evaluation at birth, a thorough medical history may provide clues to a possible genetic disorder such as Prader-Willi syndrome, in which case the baby will have varying degrees of hypotonia. A careful physical examination is warranted, including accurate measurement of the penis with palpation of the corporal bodies and testes. The goal of the initial evaluation is to ascertain whether the cause of the micropenis is central (hypothalamic/pituitary) or testicular. A central lesion may be associated with multiple hormonal defects and requires prompt recognition and treatment; a pediatric endocrinologist should be consulted immediately. Anterior pituitary function testing should be carried out, including serial measurements of serum glucose, sodium, potassium, and cortisol. Thyroid function tests should be performed. Standard karyotyping may be helpful in ruling out major chromosomal defects such as Klinefelter's syndrome.

An MRI of the head may be helpful in determining the anatomy of the hypothalamus and the anterior pituitary as well as any midline structure of the brain. Endocrine testicular function should be assessed by measuring the concentrations of serum testosterone, LH, and FSH before (baseline) and after hCG stimulation. Primary testicular failure is diagnosed by a low baseline testosterone level that persists after stimulation by hCG. A concomitant rise in basal levels of LH and FSH should be seen.[19] In cases in which testicular failure is diagnosed and the testes cannot be palpated, laparoscopy should be carried out to determine the presence of testicular tissue in the abdomen. The presence of blind-ending vas and vessels bilaterally confirms the diagnosis of vanishing testes syndrome.[18] In children with hypogonadotropic hypogonadism and impalpable testes, laparoscopy and orchiopexy should be carried out at the same setting, if possible.

Treatment

The initial management of true micropenis is dictated by the presence of associated hormonal disturbances, as seen in cases of pituitary insufficiency. In these cases, emergent correction of the biochemical abnormality is warranted. Subsequently, it is important to determine whether the penis will grow with androgen stimulation. Observation of the response to hCG during the diagnostic evaluation may give an idea of the growth potential. Further stimulation at the time of puberty may be needed (see Chapter 38). In cases in which testicular failure is a diagnosis, penile growth can be stimulated by exogenous testosterone, which can be administered intramuscularly at 3-week intervals for 4 doses.[20] Comparable results have also been obtained with the use of topical testosterone,[21] although absorption may be variable.

Controversy has arisen regarding the timing of hormonal stimulation with testosterone in patients with hypogonadotropic hypogonadism. The concern is that early testosterone treatment before puberty may stunt the normal growth at the time of puberty, as seen in animal models.[22] However, data from a study on humans suggest that normal growth of the penis can be achieved after testosterone treatment.[23]

Patients diagnosed with micropenis should be followed up through puberty with the help of a pediatric endocrinologist. Contrary to initial reports suggesting a good outcome from gender reassignment, biologic factors in the perinatal period may have a significant role in gender identification.[24] Early fetal brain imprinting by testosterone may adversely affect a person's gender identification and role as a female. On the other hand, long-term psychosexual issues may occur in the presence of a small sex organ, the main issue being whether the presence of a sizable penis is required for gender identification as well as good sexual function. Small series indicate that adults with micropenis are

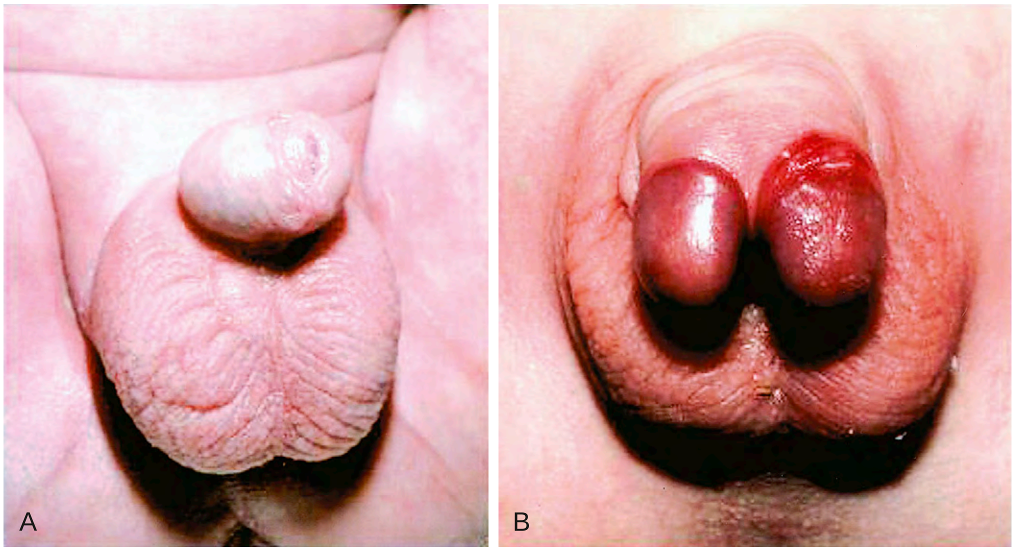

Figure 42-5 Diphallia. Appearance of external genitalia before **(A)** and after **(B)** retraction of the prepuce. (From Gyftopoulos K, Wolffenbuttel KP, Nijman RJ. Clinical and embryologic aspects of penile duplication and associated anomalies. *Urology.* 2002;60: 675-679.)

still able to establish satisfying relationships, and some have reported satisfactory sexual function.[25,26] Outcome studies in men with micropenis show that they had a longer interval between diagnosis and adulthood; they were comparable to controls in regard to gender issues, body image, social fitness, and sexuality.[27] As a result, there are insufficient data to justify female gender reassignment in a patient with micropenis.

Diphallia

The incidence of diphallia (Fig. 42-5) is 1 in 5 million live births.[28] A good embryologic explanation does not exist, given the fact that the genital tubercle is believed to arise as a single structure.

Classification

A widely accepted classification separates true diphallia from bifid phallus. These two groups are further subdivided into partial or complete duplication. True complete diphallia refers to complete penile duplication, each penis having two corpora cavernosa and a corpus spongiosum. If only one corpus is present in each penis, the term *bifid phallus* applies. This is the more commonly seen variant associated with the exstrophy-epispadias complex.

Associated Congenital Abnormalities

Associated anomalies often occur and include hypospadias, bifid scrotum, and duplication of the bladder, as seen in exstrophy.[29] Lower gastrointestinal tract and cardiac anomalies appear to be common. In a review of 77 cases (50 true diphallia, 27 bifid phallus) by Nijman, the predominant anomalies were bladder duplication (15 cases), bifid scrotum (17 cases), and imperforate anus (16 cases).[30] Although diphallia seems to be a rare, sporadic anomaly, a familial form with dominant inheritance has also been reported.[31]

Evaluation

Evaluation should include imaging of the urinary tract with a voiding cystourethrogram and upper imaging with a renal ultrasonogram. Ultrasonography may also be helpful in evaluating the phallic anatomy.[32] Cavernosography may be useful in designating the dominant phallic structures in equivocal cases. MRI can provide excellent anatomic definition and enable surgeons to formulate the optimal management plan.[10]

Treatment

Treatment of diphallia should be approached on an individual basis and should take into account the associated anomalies. Early treatment is advocated, with the goal of obtaining appropriate function (urination and erection) and adequate cosmetic results. Treatment often includes removal of one of the penises.

Buried Penis

The true incidence of buried penis (Fig. 42-6) is unknown, because there is a constant debate regarding the definition of this condition. Inconspicuous penis, hidden penis, cryptic penis, pseudomicropenis, and concealed penis have all been used as overlying terms.[33] Hidden penis was reported in 0.4% of 4.84 million newborns in the Nationwide Inpatient Sample covering 20% of hospitals in the United States from 1988 to 2000. This condition can cause recurrent balanitis and spraying of urine.[34]

A number of etiologies have been proposed: (1) failure of dartos fascia to develop into the normally elastic configuration that allows skin to slide freely on the deep layers of the shaft, (2) deficiency of penile shaft skin, (3) abnormal attachments of the tunica albuginea to Buck's fascia, (4) insufficient attachment of the dartos fascia and penile skin to Buck's fascia, (5) excessive prepubic fat pad, (6) loose skin, and (7) low position at which the crura unite to form the penile shaft.

The term *trapped penis* refers to cicatricial scarring after penile surgery, especially neonatal circumcision, which can be considered a separate entity.

Associated Congenital Abnormalities

No discrete congenital anomalies have been associated with buried penis.

Evaluation

In general, these patients have a normal scrotum with a very small-appearing penis, which becomes palpable when one presses down on the pubic fat pad and on the base of the penis.

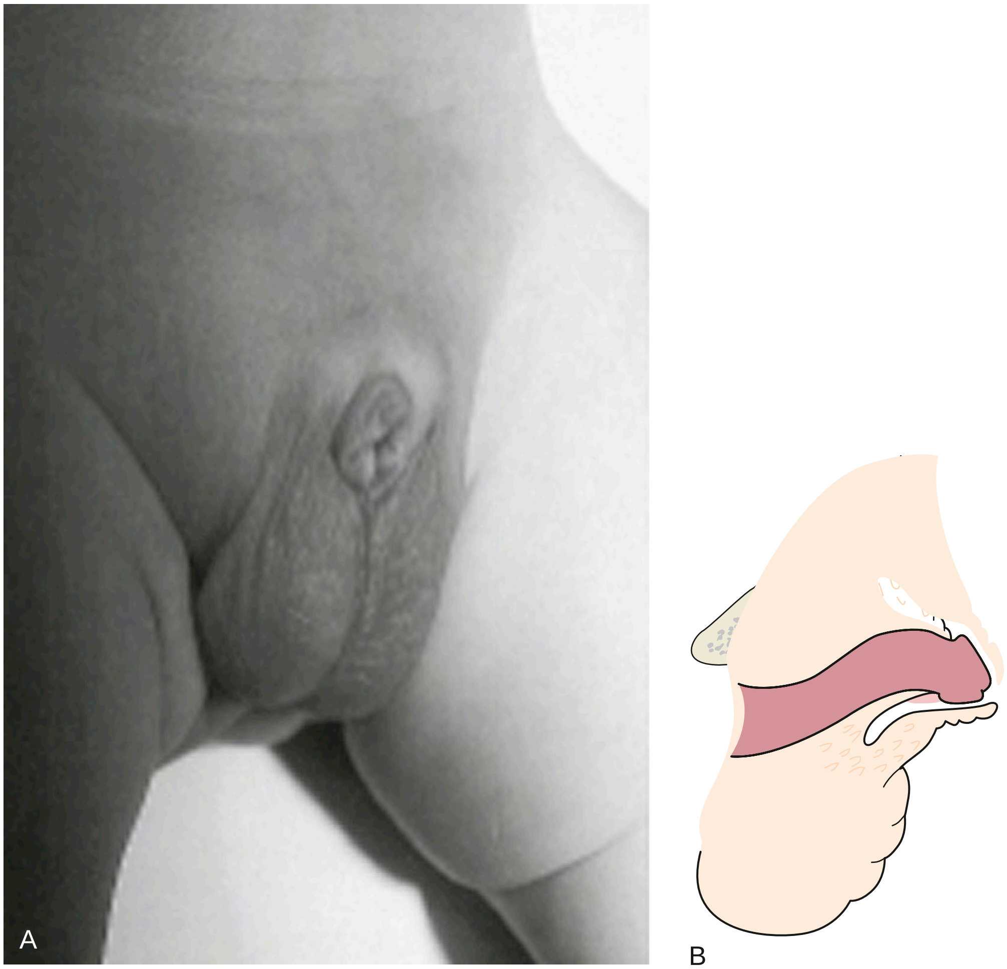

Figure 42-6 Physical appearance **(A)** and schematic view **(B)** of a buried penis. (From Shankar KR, Rickwood AM. The incidence of phimosis in boys. *BJU Int.* 1999;84:101-102.)

During examination, it is important to determine whether the glans can actually be pushed out of the foreskin by trying to retract the skin over the glans.

Treatment

The indications for and timing of surgery are controversial and may depend on the cause (Table 42-2). Indications for surgery include difficulties with hygiene, phimosis, balanitis, and psychosocial stressors. Current recommendations are to perform surgical correction after the child has started to walk and has lost most of the prepubic fat pad. Often, buried penis is secondary to obesity, and treatment of this underlying condition takes precedence. Watchful waiting is an option, but spontaneous resolution does not always occur.

The main complications after surgical correction include recurrent buried penis and redundant penile skin.[34] This surgery can be performed safely in children from 3 months of age.

Webbed Penis

Webbed penis (Fig. 42-7) is rarely an isolated congenital anomaly. In this condition, a web or fold of skin obscures the penoscrotal angle. It can be iatrogenic, occurring after circumcision or penile surgery. Alternatively, it is postulated that a disturbance in the development of the prepuce may leave the ventral penis with inadequate skin coverage, resulting in borrowing of scrotal tissue.[35]

Associated Congenital Abnormalities

Webbed penis commonly occurs in conjunction with hypospadias, chordee, hydroceles, or micropenis.[36]

Treatment

Surgical repair is recommended only if the cosmetic appearance is of great concern.[37] Many descriptions of surgical repair have been published, including simple incision, excision of redundant skin with closure, multiple Z-plasties, and excision of skin with mobilization of triangular skin flaps. Rarely, the urethra is hypoplastic, requiring urethral surgery in conjunction with skin rearrangement.

Phimosis

The incidence of true pathologic phimosis (Fig. 42-8) has been estimated to be 0.4 cases per 1000 boys per year.[38] The incidence cannot be clearly determined, because a certain proportion of boys of any age group have a physiologic nonretractable foreskin. Oster found phimosis in 96% of boys at birth, in 80% at 6 months, and in 50% at 3 years.[39] These numbers are comparable to those recorded by Herzog and Alvarez.[40] This should

Table 42-2 **Causes of Buried Penis**

Etiology	Surgical Intervention	Timing
Trapped penis	Revision of circumcision, with removal of scar tissue; Z-plasty with local flaps may be needed	Whenever possible (usually after 4 mo)
Abnormal dartos attachments	Penile degloving with release of tethering tissues and fixation of penile skin dermal layer to deep tunica albuginea of penile shaft	If indicated*
Excessive prepubic fat pad	Potential panniculectomy and penile degloving, as above	If indicated*
Abnormal skin attachments	Penile degloving, as above	If indicated*

*Indications for surgery include difficulties with hygiene, phimosis, balanitis, and psychosocial stressors.

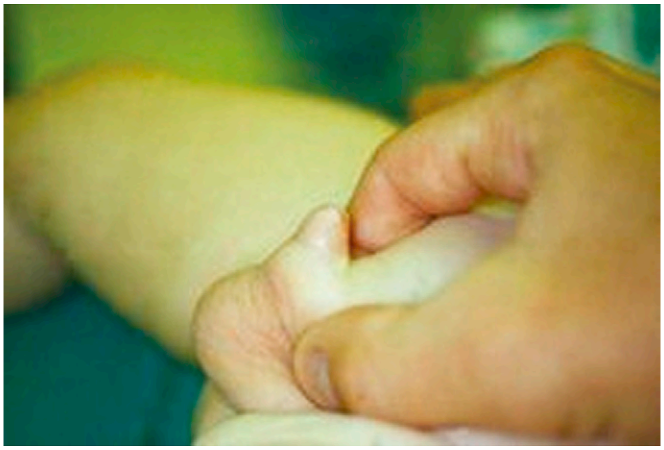

Figure 42-7 Webbed penis. A fold of skin obscures the penoscrotal angle.

be considered a physiologic phimosis that resolves with time. Physiologic phimosis occurs as the normal prepuce gradually becomes detached from the glans with keratinization of the epithelial layers, aided by smegma.[41] True pathologic phimosis includes balanitis xerotica obliterans (BXO) with scar tissue involving a portion of the prepuce; occasionally, recurrent fungal infection prevents preputial retraction.

Classification

Table 42-3 describes the classification of phimosis.

Treatment

There is still considerable debate on the handling of phimosis. True pathologic phimosis requires a circumcision. Physiologic phimosis can be simply observed; the age at resolution is an uncertainty, although the vast majority resolve. Recent data showed efficacy for a 6-week course of topical steroids in up to 87% of boys ages 1 to 16 years.[42] Parents of boys who are uncircumcised should be encouraged to teach their sons to gently retract their foreskins by age 3 years.

Curvature of the Penis

Curvature of the penis constitutes 8.6% of congenital penile anomalies, second only to hypospadias (68%), and has a reported incidence of 0.6% at birth[43] (Fig. 42-9). It is usually not recognized until later in childhood, because the penis appears abnormal only with erection.[44]

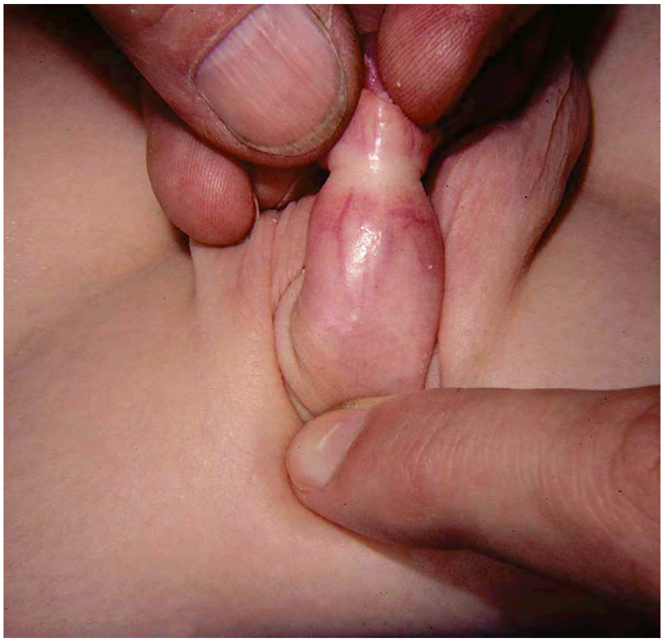

Figure 42-8 Phimosis. A tight phimotic ring prevents exposure of glans.

Curvature of the penis is thought to be caused by asymmetry in the compliance of the tunica albuginea of the corpora cavernosa as a result of developmental arrest during embryogenesis.[45,46] The curvature may be either lateral or medial. Medial curvature is usually associated with hypospadias and is referred to as chordee. Minor penile curvature may be the result of ventral penile skin deficiency and should be distinguished from corporal anomalies.

Treatment

At the time of surgical repair, use of the Gittes artificial erection test will determine the degree of curvature.[47] The goal of surgical correction is to achieve corpora of similar size. Various techniques have been described, ranging from complete penile disassembly, to corporal rotation, to use of free dermal or tunica vaginalis grafts, to simple degloving and plication.[48-50]

Table 42-3 Classification of Phimosis

Category	Description
	A. Retractability of Foreskin
0	Full retraction
1	Full retraction of foreskin and tight behind the glans
2	Partial exposure of glans
3	Partial retraction, meatus just visible
4	Slight retraction, but distance between tip and glans (neither meatus nor glans can be exposed)
5	Absolutely no retraction
	B. Appearance of Foreskin
0	Normal
1	Crack in prepuce and skin splitting on gentle retraction
2	Small, partially circumferential white scar
3	Balanitis xerotica obliterans or severe scarring

From Atilla MK, Dundaroz R, Odabas O, et al: A nonsurgical approach to the treatment of phimosis: local nonsteroidal anti-inflammatory ointment application. *J Urol.* 1997;158:196-197.

Penile Torsion

Torsion of the penis is reported to be common, although its incidence as an isolated condition is unknown. Usually, the torque is in a counterclockwise direction toward the left. Penile torsion may be caused by an abnormal arrangement of the penile shaft skin early in development, secondary to aberrant attachments of the suspensory ligaments at the base of the penis. Pressure from the heel of the fetus during early development may also play a role.

Associated Congenital Abnormalities

An anatomically normal penis is present, but the urethral meatus may be in an abnormal position. Penile torsion is seen with hypospadias or abnormalities involving the penile skin shaft, usually in cases in which the median raphe spirals obliquely around the shaft and seems to insert not at the base of the glans below the urethral meatus but somewhat atypically.

Treatment

Neonatal circumcision is discouraged if surgical repair is being considered and can be carried out at the time of the repair. Surgical repair is indicated in severe torsion of the penis in which the glans is in an abnormal position. In a milder form of penile torsion, the penile skin can be taken down and simply sewn back in such a way as to anchor the glans in a normal configuration in conjunction with circumcision. More severe penile torsion may require a more thorough degloving of the penis and mobilization of its base to remove a band of scar tissue that may be responsible for the abnormal configuration of the penile skin shaft. Anchoring sutures at the base of the penis may also help reorient the penis.[50] A modified Nesbit plication has been reported, as well as a dorsal dartos flap rotation after degloving (Fig. 42-10).[51]

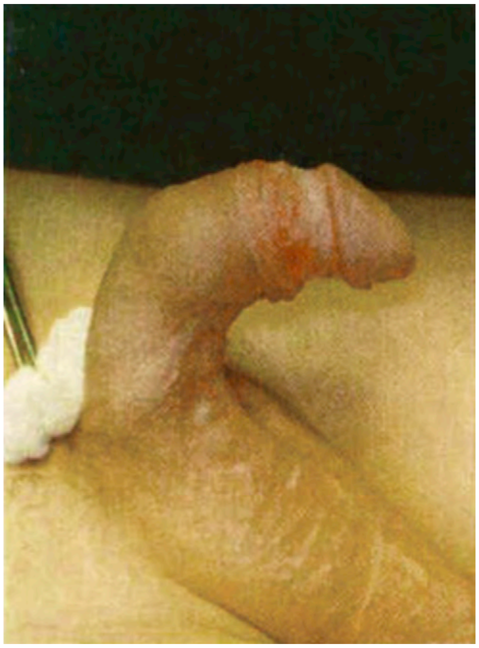

Figure 42-9 Penile curvature. (From Perovic SV, Djordjevic ML, Djakovic NG. A new approach to the treatment of penile curvature. *J Urol.* 1998;160(3 Pt 2):1123-1127.)

Penile Cysts: Parameatal, Median Raphe, and Epidermal Inclusion Cysts

Parameatal cysts and median raphe cysts are rare; epidermal inclusion cysts (Fig. 42-11) can be quite common. Parameatal cysts are seen usually seen at birth, after circumcision, in the form of a small blister adjacent to the urethral meatus and may result from occlusion of a periurethral duct. Median raphe cysts are caused by incomplete fusion of the urethral folds, abnormal formation of epithelial buds from the urethral epithelium that then became sequestrated and independent after closure of the medium raphe, and cystic dilations of ectopic Littre's periurethral glands.[52] Epidermal inclusion cysts commonly occur after penile surgery and result when islands of epithelium are left behind in the subcutaneous tissue.

Classification

Median raphe cysts can occur anywhere from the meatus to the anus. They can be glomus tumors, dermoid cysts, pilonidal cysts, epidermal cysts, urethral diverticula, or steatocystomata.[53]

Treatment

Aspiration and simple drainage may carry a risk of recurrence. Simple complete excision followed by primary closure has generally been regarded as the treatment of choice.[54] If no malignancy is evident, simple observation may be the best treatment option.

Meatal Stenosis

Meatal stenosis is one of the most common complications after circumcision and has been reported in up to 7.3% of circumcised patients presenting to a pediatrician.[55] It can also occur in patients with coronal or subcoronal hypospadias who have undergone hypospadias repair or, rarely, BXO. Meatal ischemia secondary to ligation of the frenular artery during circumcision or recurring meatitis and local irritation at the junction of

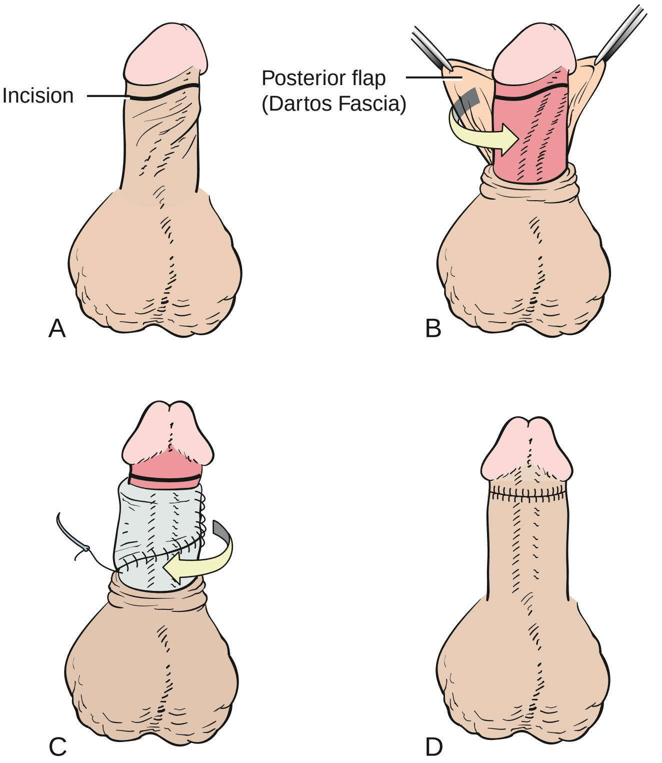

Figure 42-10 **A** through **D,** Dartos flap rotation after degloving. (From Fisher C, Park M. Penile torsion repair using dorsal dartos flap rotation. *J Urol.* 2004;171:1903-1904.)

the glans epithelium and urethral mucosa are thought to lead to meatal stenosis.[55] The cardinal symptoms include penile pain at micturition; a narrow, high velocity stream; and the need to sit or stand back from the bowl to urinate, secondary to a deflected stream.

Treatment

Meatotomy can be performed in the office after topical application of anesthetic cream (EMLA or LMX) for 30 to 45 minutes. A straight crushing hemostat can be used for 1 to 2 minutes along the ventral web with subsequent incision.[56]

SCROTAL ANOMALIES

Congenital Absence and Hypoplasia

Complete absence of the scrotum (Fig. 42-12) is extremely rare, with only four cases reported. It is caused by failure of the labioscrotal fold to develop.

Associated Congenital Abnormalities

Facial anomalies, developmental delay, nystagmus, clinodactyly, cardiac septal defects, anterior displaced anus, and clubfoot have all been reported, but the frequencies are unknown because of the small number of cases. Maldescended testicle is common with scrotal hypoplasia.[57]

Evaluation

A thorough maternal and family history may demonstrate a possible teratogen exposure or other etiologic factor. Attempting to identify the location of the testes and other congenital anomalies is essential for long-term management. MRI can be helpful to localize the testes.[58]

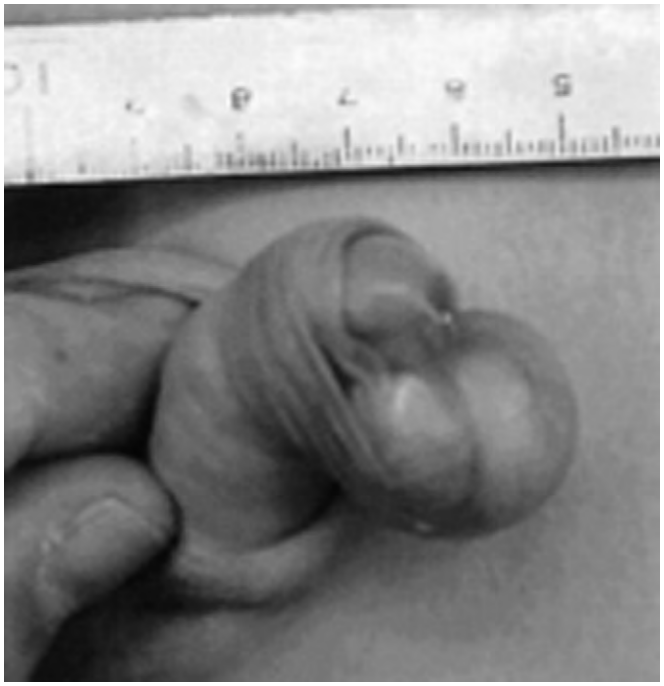

Figure 42-11 Epidermal inclusion cyst of the penis. (From Suwa M, Takeda M, Bilim V, Takahashi K. Epidermoid cyst of the penis: a case report and review of the literature. *Int J Urol.* 2000;7:431-433.)

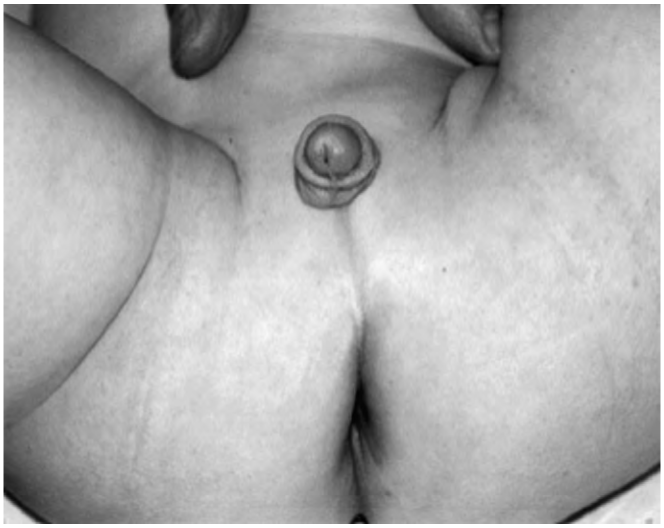

Figure 42-12 Epidermal inclusion appearance of child with congenital scrotal agenesis. Note normal median raphe and morphology of the penis, with flat perineal skin and absence of rugated tissue. (From Janoff DM, Skoog SJ. Congenital scrotal agenesis: description of a rare anomaly and management strategies. *J Urol.* 2005;173:589-591.)

Treatment

With agenesis, neoscrotal construction should be preferentially performed using a preputial skin flap.[57] If the child is circumcised, perineal tissue expanders offer an alternative. Orchiopexy may be performed during or after construction.

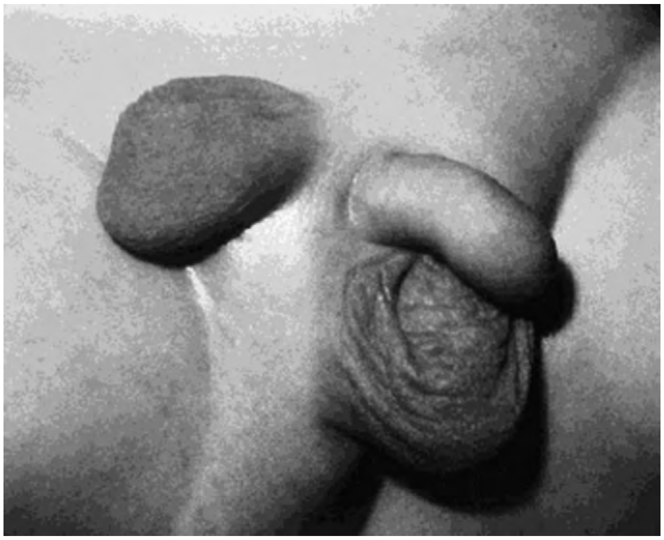

Figure 42-13 Ectopic scrotum: normal left hemiscrotum with ectopic right inguinal scrotum and testes. (From Hoar RM, Calvano CJ, Reddy PP, et al. Unilateral suprainguinal ectopic scrotum: the role of the gubernaculum in the formation of an ectopic scrotum. *Teratology.* 1998;57:64-69.)

Ectopic Scrotum

Ectopic scrotum (Fig. 42-13) is extremely rare, with approximately 22 cases reported in the literature. Two theories have been proposed to account for this anomaly: (1) abnormalities in the development of the gubernaculum with its secondary attachment to the skin covering the genital tubercle, and (2) failure of fusion of the outer genital folds secondary to heel compression during intrauterine life.[59]

Associated Congenital Abnormalities

Ectopic scrotum has been seen in association with cleft lip or palate, testicular maldescent, inguinal hernias, patent urachus, imperforate anus, bladder exstrophy, and skeletal/limb defects.[59-61] Elder and Jeffs reported a high incidence of ipsilateral renal anomalies such as renal agenesis.[62]

Evaluation

Careful physical examination to localize the testes and upper urinary tract imaging with ultrasonography are recommended.

Treatment

Various methods have been described, including excision of the ectopic hemiscrotum with mobilization of the testes into the opposite hemiscrotum, reconstruction by perineal Z-plasty, perineal full-thickness flaps, and rotation of the ectopic scrotum into its native position with suturing to the lateral aspect of the normotopic scrotum.[63,64]

Penoscrotal Transposition

Penoscrotal transposition (Fig. 42-14) is usually associated with other anomalies. Abnormal positioning of the genital tubercle in relation to the labioscrotal swellings during the critical fourth to fifth week of gestation may affect the inferomedial migration and fusion of the scrotal swellings. If the phallic tubercle also is intrinsically abnormal, development of the corporal bodies and the urethral groove and folds may be affected; this explains the frequent occurrence of the other genital abnormalities.[65] Some reports suggest a chromosomal etiology. In a review of 53 patients, 13% had a familial link.[66]

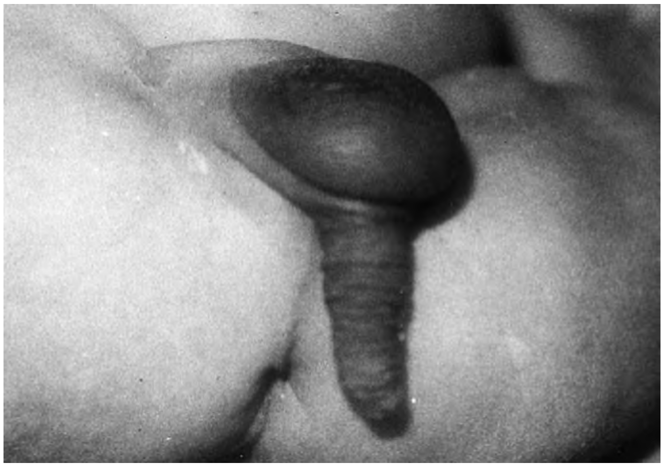

Figure 42-14 Complete penoscrotal transposition. (From Chadha R, Mann V, Sharma A, Bagga D. Complete penoscrotal transposition and associated malformations. *Pediatr Surg Int.* 1999;15:505-507.)

Classification

Penoscrotal transposition is also referred to as doughnut scrotum, prepenile scrotum, and Shawl scrotum. It can be complete, with the penis covered entirely by the scrotum, or incomplete, in which case the scrotum does not fuse above the penis.

Associated Congenital Abnormalities

There is a high incidence of associated anomalies. Renal dysplasia or agenesis, imperforate anus, central nervous anomalies, cardiac abnormalities, and upper-limb defects have been reported. Some small series have reported associated anomalies in up to 100% of patients, but the largest review to date found that 32% had associated organ system anomalies.[66] The genitourinary system was most commonly affected, with vesicoureteral reflux occurring in 9%. Most patients with penoscrotal transposition had an associated hypospadias (79%) or chordee (81%).

Evaluation

Most nonrenal organ system anomalies are clinically apparent. A renal ultrasonogram is recommended in the evaluation of these patients, given the high rate of associated renal defects. Prenatal ultrasound at 35 weeks has also been shown to detect this anomaly[67] (Fig. 42-15).

Treatment

Repair of penoscrotal transposition can be carried out at the time of hypospadias repair or at a different time. Timing of the surgery should correspond to that of the genital surgery (before 18 months of age). Several techniques for scrotoplasty have been described. The aim of the procedure is to free the penis by moving the skin flaps (Fig. 42-16).

In general, the relocation of the scrotum to a normal dependent position relies on mobilizing the two halves of the scrotum that circumscribe the penis and then moving the penis away. In more incomplete forms of penoscrotal transposition, a simple Y-V-plasty at the level of the dorsal aspect of the penoscrotal junction may allow the penis to move out of the scrotum. In more complex forms of transposition, a circumferential incision can be made bilaterally around the superior aspect of the scrotum and penis. These incisions can then be carried out on the other side of the penis, allowing the penis to be moved out of the scrotum. However, these techniques may result in deficiency of the ventral shaft skin. During the repair, care must be taken not to injure the contents of the scrotum, especially the spermatic cord. Tissue planes can be developed by injecting the subcutaneous tissue with a solution of lidocaine with epinephrine, which also helps to reduce blood loss.

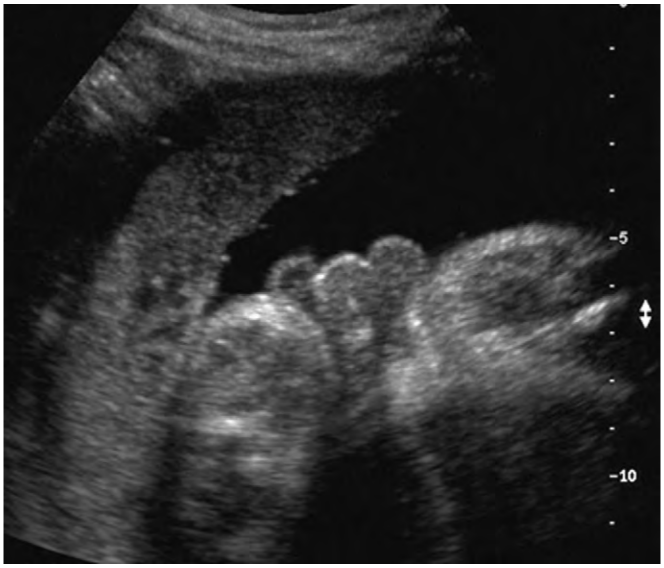

Figure 42-15 Prenatal diagnosis of penoscrotal transposition. Axial ultrasound scan shows the penis between the caudal aspects of the bifid scrotum. (From Gotoh M, Tsai S, Sugiyama T, et al. Giant scrotal hemangioma with azoospermia. *Urology.* 1983;22:637-639.)

Bifid Scrotum

Approximately 5% of patients with posterior hypospadias have a bifid scrotum.[68] Bifid scrotum (Fig. 42-17) occurs along the same spectrum as penoscrotal transposition, with abnormal positioning of the genital tubercle in relation to the labioscrotal swellings. However, the labial scrotal folds are completely separated, and no median raphe is present.

Associated Congenital Abnormalities

Renal cysts, vesicoureteral reflux, undescended testicles, heart malformations, and skeletal or limb defects are seen in posterior hypospadias, but there have been no discrete series on anomalies associated with isolated bifid scrotum.

Evaluation

A renal ultrasonogram is recommended, given the risk of renal abnormalities.

Treatment

Surgical repair is usually carried out at the time of hypospadias repair. It is performed in a manner similar to penoscrotal transposition, and rotation of flaps of scrotal tissue may be required.

Scrotal Hemangioma

Genital hemangioma accounts for approximately 1% of all hemangiomas.[69] Fifty cases have been reported in the literature, although the distinction between the two subtypes is not always mentioned.[70] Awakura and coworkers reported 37 cases specific to Japan.[71] Table 42-4 lists the types and causes of scrotal hemangioma.

Associated Congenital Abnormalities

Cases have been reported with Klippel-Trenaunay syndrome and bladder tumors.[72]

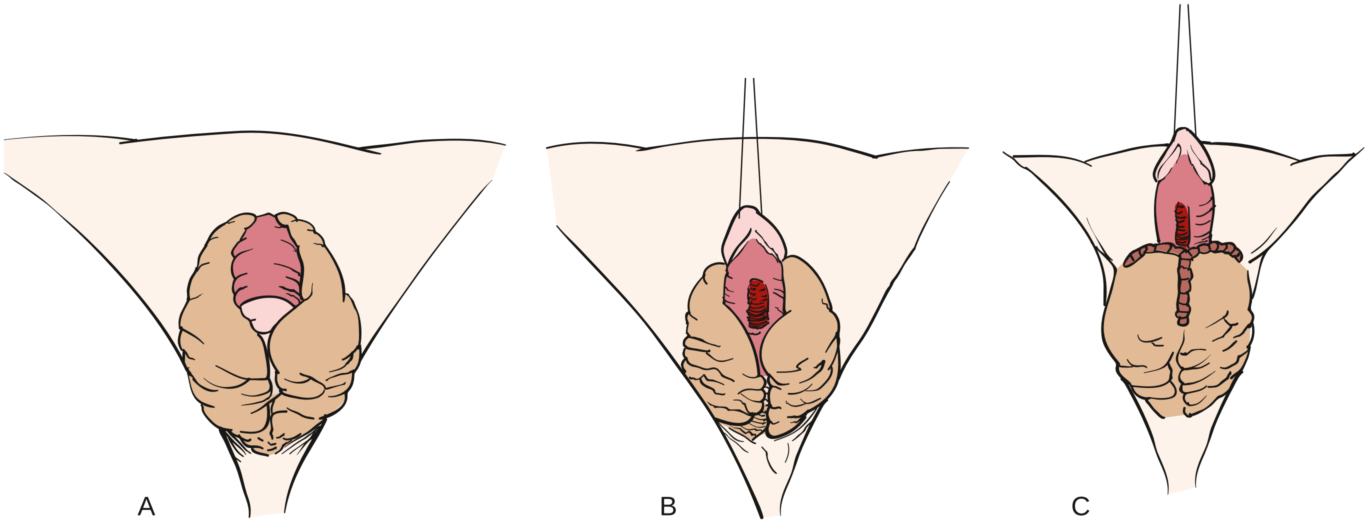

Figure 42-16 Glenn-Anderson repair: bilateral rotational advancement flaps with relocation of the scrotal compartment. (From Glenn JF, Anderson EE. Surgical correction of incomplete penoscrotal transposition. *J Urol.* 1973;110:603-605.)

Evaluation

Cutaneous hemangiomas are fairly evident on examination. Cavernous hemangiomas (Fig. 42-18) require careful delineation, because scrotal arteriovenous malformations have also been reported in association.[73] Scrotal ultrasound may be useful in delineating the extent of the mass. Because an absence of flow on Doppler studies does not exclude the diagnosis of hemangioma, MRI may provide more useful information for differentiation of scrotal hemangioma from other lesions (Fig. 42-19).[74]

Idiopathic Scrotal Edema (Genital Lymphedema)

Idiopathic penile/scrotal edema most commonly affects prepubertal boys (ages 5 to 11 years).[75] Najmaldin and Burge reported this entity as the second most common cause of "acute scrotum," accounting for 30% of their admissions,[76] whereas Markou's group reported an incidence of only 8% among 100 boys presenting with acute scrotum.[77]

This is a self-limited disorder in which scrotal erythema and edema occur. The cause is unknown, although it is probably a variant of angioneurotic edema.[77]

Evaluation

Patients usually have no symptoms except for minimal scrotal discomfort which causes a waddling gait. Edema can affect the penis, the perineum, and the inguinal region. In a recent series by Klin and associates, 90% of the patients had unilateral involvement, and the duration of symptoms was from 2 to 72 hours.[78]

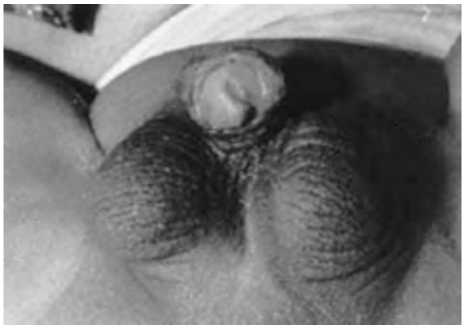

Figure 42-17 Bifid scrotum. (From Chadha R, Gupta S, Mahajan JK, Kothari SK. Two cases of pseudoduplication of the external genitalia. *Pediatr Surg Int.* 2001;17:572-574.)

The testes may not be palpable owing to the extent of the edema, making diagnosis uncertain and leading to surgical exploration. Evaluation by scrotal ultrasonography can help differentiate the testes and ascertain their blood flow. Characteristic sonographic features include marked thickening of the scrotal wall, increased peritesticular blood flow, and mild reactive hydrocele.

Treatment

The edema usually resolves within 72 hours, but up to 20% of patients experience some type of recurrence.[79] Management includes reassurance, activity restriction, scrotal support, and close observation. The process resolves without long-term sequelae.

Splenogonadal Fusion

Approximately 150 cases of splenogonadal fusion have been reported in the literature.[80] Continuous and discontinuous forms occur with equal frequency[81] (Table 42-5). Most of the reported patients were younger than 20 years old; fusion was found on the left side in 98%, and 95% of the patients were male.

The cause is unclear. For some unknown reason, the two organs fuse during the 5th to 8th week of embryonic life. During this period, the splenic anlage and the left urogenital fold that contains the gonadal mesoderm are in close proximity. This explains the high incidence of limb defects. The discontinuous form (Fig. 42-20) may represent a rare variant of accessory spleen.[82]

Associated Congenital Abnormalities

The most common defects involve the limbs. Other associated anomalies include micrognathia, cardiac defects, cleft palate, anal defects, spina bifida, cryptorchidism, hypospadias, and facial muscle agenesis. Eight patients have been reported with bilateral cryptorchidism.[83]

Evaluation

Exploration is commonly performed to look for an undescended testicle, inguinal hernia, or scrotal mass. Although ultrasonography can reliably demonstrate the extratesticular

Table 42-4 **Causes of Hemangioma**

Type	Cause	Presentation	Treatment Options
Cutaneous (strawberry) hemangioma	Proliferation of immature capillary cells within skin, which may be under hormonal influence.	May occur at any age. Most growth occurs over 3-6 mo. May involute spontaneously.	1. Oral therapy with short-duration steroids 2. KTP laser therapy 3. Surgical excision
Subcutaneous (cavernous) hemangioma	Familial cases suggest that inheritance may occur in an autosomal dominant fashion. They consist of numerous vascular spaces of varying size lined with epithelial cells.	Lesions manifest within the first 2 decades of life and grow. They manifest as scrotal enlargement with the overlying skin being rugose or bosselated. On examination, they have the typical "bag of worms" sensation but are more firm. They are usually painless. The testes and epididymis are normal on examination.	Surgical en bloc excision is recommended secondary to the possibility of traumatic rupture or hemorrhage, although this is rare. Another compelling argument is based on reports of decreased testicular size and possible infertility.

KTP, potassium titanyl phosphate.

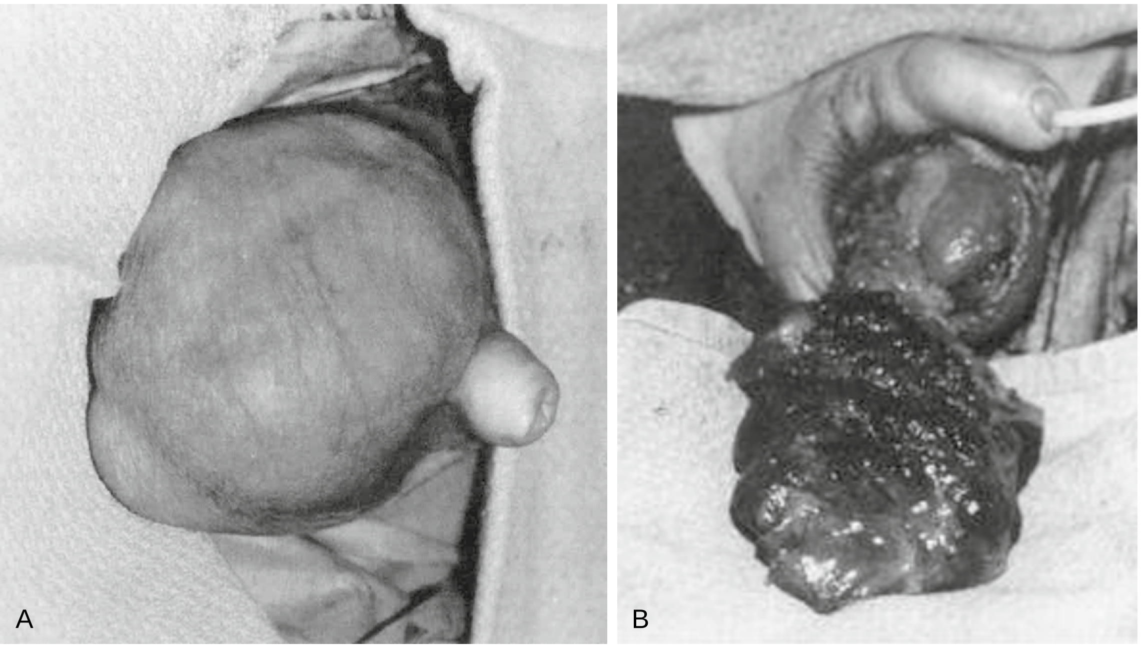

Figure 42-18 Preoperative **(A)** and postoperative **(B)** views of cavernous hemangioma. (From Ferrer FA, McKenna PH. Cavernous hemangioma of the scrotum: a rare benign genital tumor of childhood. *J Urol.* 1995;153:1262-1264.)

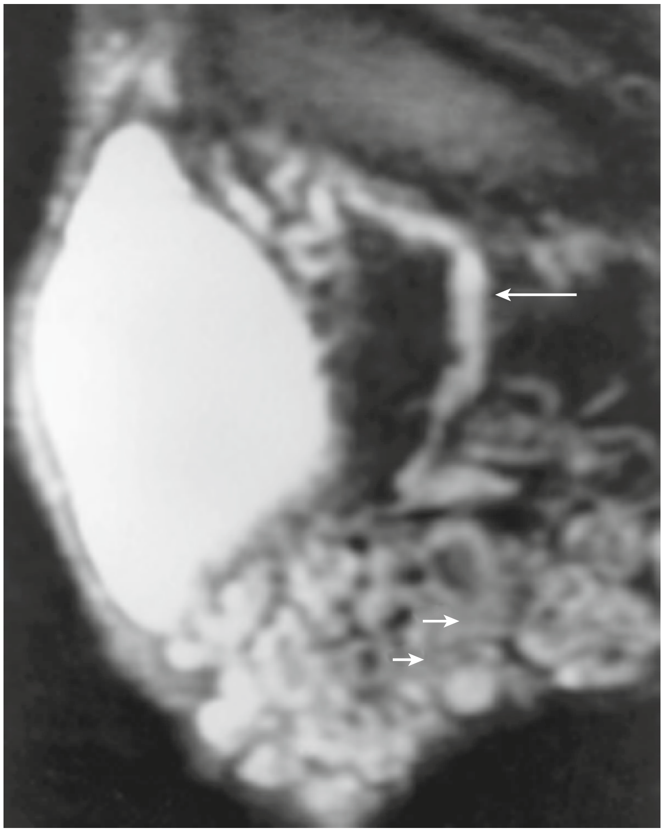

Figure 42-19 Scrotal hemangioma. Sagittal magnetic resonance image shows mass of lower scrotum, dilated testicular vein, *(long arrow)*, and punctuate foci of hypointense thrombi *(short arrows)*. (From Aizenstein RI, Wilbur AC, O'Neil HK, Gerber B. Clinical image: MRI of scrotal hemangioma. *J Comput Assist Tomogr*. 1996;20:888-889.)

location of a palpable mass, it cannot provide a definitive histologic diagnosis. Scintigraphy with a technetium 99m (^{99m}Tc) sulfur colloid can identify ectopic uptake within the scrotum or tail of the functioning splenic tissue and add specificity to the imaging diagnosis.[84]

Treatment

Surgical exploration is generally needed to rule out malignancy, but orchiectomy is usually not indicated, because the splenic tissue can be dissected away from the tunica albuginea in most cases.[85] Laparoscopic management has also been performed during exploration for intra-abdominal testes.[86]

ACUTE SCROTUM

The presentation of acute scrotal complaints in pediatric patients requires urgent attention by the physician. *Acute scrotum* is defined as the sudden onset of scrotal pain, which can be accompanied by swelling, erythema, and systemic signs of illness. The differential diagnosis is extensive. A delay or error in diagnosis may lead to irreversible damage or ischemic necrosis of the testicle due to torsion of the spermatic cord. However, up to 70% of cases of acute scrotum have pathology that does not require surgery.[87] A 2-year retrospective review of 238 cases of acute scrotal pain encountered in a children's hospital emergency department demonstrated that the incidences of testicular torsion, torsion of a testicular appendage, and epididymitis were 16%, 46%, and 35%, respectively.[88] Diagnostic errors can be avoided if one approaches the patient with an understanding of each of the possible causes of scrotal pathology. Careful evaluation and expeditious management are essential in today's litigious society.

Clinical Presentation

The history and physical examination can significantly narrow the differential diagnosis of acute scrotum (Table 42-6). The combined background information and physical findings can frequently suggest the correct diagnosis.[89] The age of the patient is important. Testicular torsion is most common in neonates and postpubertal boys, although it can occur in males of any age. The onset and duration of the pain must be carefully determined. Torsion can manifest with sudden or gradual onset of severe testicular pain. Nausea, vomiting, and fever may occur, but urinary symptoms are unusual.[90] A history of trauma does not exclude the diagnosis. Recurrent severe pain of rapid onset and spontaneous resolution is suggestive of intermittent torsion.[91] The physician needs to be aware that an embarrassed child may state that he has lower abdominal pain or inguinal pain rather than scrotal pain.

Physical Examination

A general abdominal examination should be performed, with particular attention given to flank tenderness and bladder distention. Next, the inguinal regions should be examined for obvious hernias and any swelling or erythema. The genital examination begins with inspection of the scrotum. The two sides should be assessed for discrepancies in size, degree of swelling, presence and location of erythema, thickening of the skin, and position of the testes. A high-riding testis with an abnormal (transverse) lie may suggest torsion, but this diagnosis is unlikely if pain has been present for longer than 12 hours and the scrotum has a normal appearance. Torsion of a maldescended testicle manifests as a swollen, very tender mass high in the groin in association with an empty hemiscrotum. Adequate physical examination may not be possible if the patient refuses to be touched. Fever and an elevated white blood cell count are seldom associated with testicular torsion.

The cremasteric reflex should always be assessed. The normal reflex consists of cremasteric contraction with elevation of the testis on stroking or gentle pinching of the medial thigh. In 1984, Rabinowitz made the remarkable observation that loss of the cremasteric reflex is a 100% sensitive test for the presence of torsion.[92] The specificity, however, was only 66%, because the reflex can be absent in a number of other conditions, such as cryptorchidism and myelomeningocele, as well as in normal individuals. In a study of 225 normal boys, the reflex was present in 48% of newborns, 45% of boys between 1 and 30 months of age, and 100% of boys between 30 months and 12 years.[93] There have been rare instances of testicular torsion with an intact cremasteric reflex.[94]

Table 42-5 Classification of Splenogonadal Fusion

Continuous fusion	Connection of the spleen and the gonad by a cord of splenic or fibrous tissue
Discontinuous fusion	Ectopic splenic tissue attached to the gonad without connection to spleen

Differential Diagnosis

Vascular Causes

TESTICULAR TORSION

Testicular torsion or torsion of the spermatic cord is a surgical emergency. This condition results from an abnormally mobile testicle twisting on its vascular pedicle (the spermatic cord),

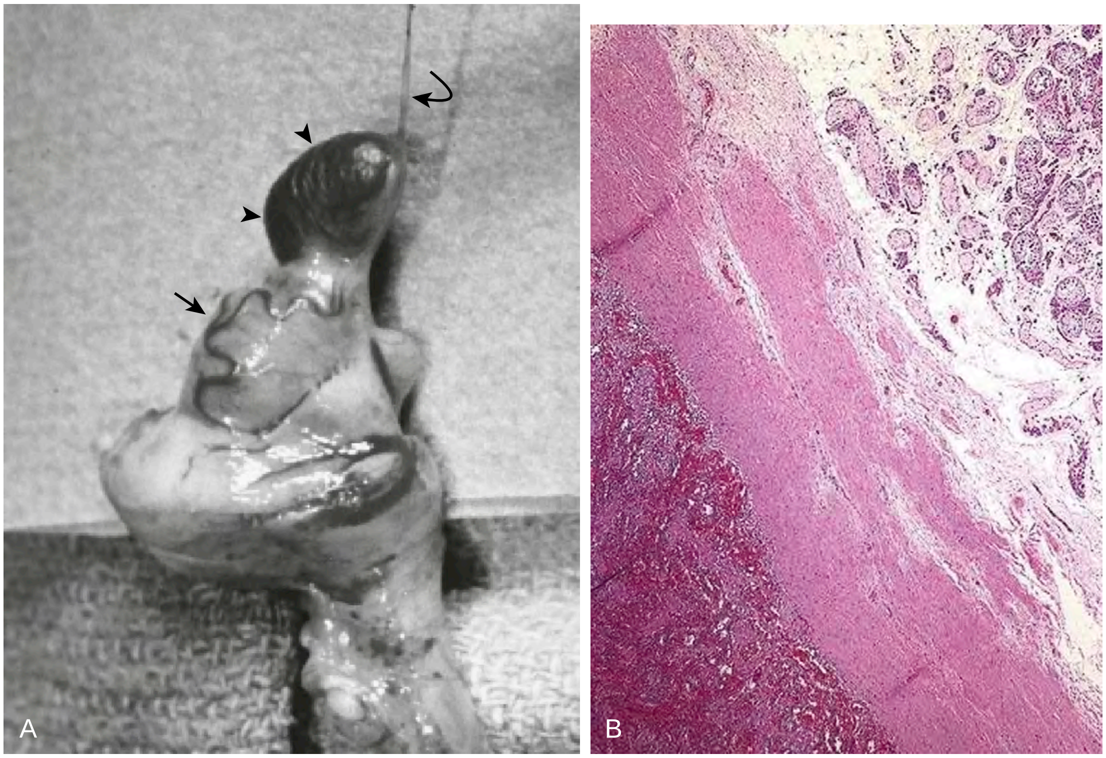

Figure 42-20 **A,** Discontinuous splenogonadal fusion: left testicle with ectopic spleen *(arrows)* attached to the upper pole. **B,** Seminiferous tubules can be seen on the upper left, and splenic tissue is present on the lower right. (**A,** From Cirillo RL Jr, Coley BD, Binkovitz LA, Jayanthi RV. Sonographic findings in splenogonadal fusion. *Pediatr Radiol.* 1999;29:73-75. **B,** Courtesy of Dr. Dharam M. Ramnani.)

Table 42-6 Differential Diagnosis of Acute Scrotum

Vascular	Inflammatory	Rare
Henoch-Schönlein purpura Testicular torsion Torsion of vestigial appendages Trauma Varicocele	Epididymitis Idiopathic scrotal edema Orchitis	Appendicitis Familial Mediterranean fever Hydrocele Inguinal hernia Lymphangioma Spermatocele Tumors Thrombophlebitis Ventriculoperitoneal shunt herniation

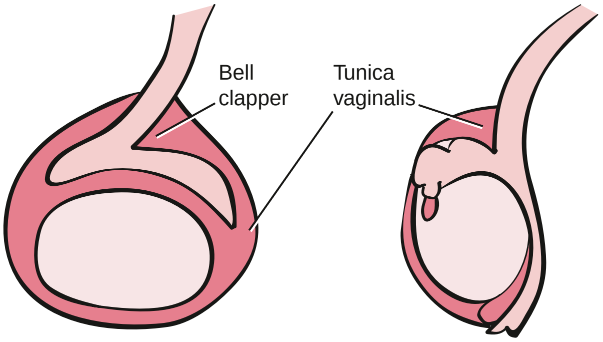

Figure 42-21 Abnormal *(left)* and normal *(right)* insertion of the tunica vaginalis. (From Dogra V. Bell-clapper deformity. *Am J Roentgenol*. 2003;180:1176.)

causing obstruction to the gonads' blood supply. According to some authors, up to 80% of subjects with acute pain and scrotal swelling have torsion,[95] although the figure is probably closer to 25% to 35%.[96] The peak incidence is between 12 and 16 years of age.[97] Early recognition and prompt operation are necessary if the testicle is to survive the ischemic insult.

Testicular torsion may occur within or outside the tunica vaginalis. Torsion within the tunica vaginalis is termed *intravaginal torsion;* it results from an abnormally high investment of tunica on the spermatic cord within the scrotum, termed the *bell-clapper deformity*.[98] It is found in 12% of testes at postmortem examination and frequently occurs bilaterally.[99] It is the most common cause of torsion in adolescents. *Extravaginal torsion* is the result of nonfixation of the testis, cord, or processus vaginalis within the scrotum, which allows for hypermobility of the testicle, thus predisposing to twisting.[100] This situation is seen almost exclusively in newborns. Approximately 10% of all torsion episodes occur in newborns. Risk factors for extravaginal torsion include multiparity, excessive uterine pressure, and a strong cremasteric contraction[101] (Fig. 42-21).

The testis may twist from three-quarters of a turn (270 degrees) to two complete turns (720 degrees). If torsion is 180 degrees or less, diminished flow is seen. Twisting of the spermatic cord initially leads to venous obstruction and swelling. Subsequently, arterial occlusion causes hemorrhagic infarct. Despite the general teaching that torsion occurs in the medial direction, in a significant number of instances (33%) it occurs in the lateral direction.[102] As a result, some groups have recommended that scrotal ultrasonography accompany manual detorsion to confirm satisfactory outcome.

No singular or combined examination or test provides a definitive diagnosis with 100% accuracy, short of surgical exploration.[103] Routine exploration of the acute scrotum has been reported to be negative for torsion in almost 50% of cases.[104] A scoring system based on pain present for 6 hours or less, decreased or absent cremasteric reflex, and diffuse tenderness can aid in clinical decision making. Testicular torsion was diagnosed in 85.7% of patients who had all three of these symptoms, whereas no torsion was diagnosed in those patients with none of these symptoms.[105] Sonography has been shown to be a very helpful adjunctive diagnostic study that reduces the number of emergency scrotal explorations. Over a 6-year period, sonography decreased the rate of scrotal exploration from 92% to 8% in patients presenting with acute scrotal pain and swelling.[106] In the setting of equivocal or low probability for torsion, color Doppler ultrasound demonstrated 88.9% sensitivity and 98.8% specificity for identification of torsion. There is some evidence that serum markers may play a role in differentiating testicular torsion from inflammatory conditions. Interleukin-6 is significantly elevated in epididymitis compared with torsion.[107]

At the present time, the decision to operate on a patient with an acute scrotum should be primarily based on the history and physical findings, not on the laboratory or imaging findings. Immediate exploration should be performed even if the symptoms have lasted longer than 36 hours, because variability in the degree of torsion may allow for salvage. A salvage rate of almost 100% exists within the first 6 hours after the onset of symptoms, a 70% rate between 6 and 12 hours, and a 20% rate between 12 and 24 hours.[102] Manual detorsion is an option for initial management; it allows for potential testicular salvage but should be followed by immediate surgical exploration and bilateral scrotal orchiopexy.[108] There is still controversy in the literature as to whether a retained ischemic testicle could expose the patient to potential autoimmunization and consequent damage to the contralateral gonad, impairing fertility.[109] Furthermore, use of either absorbable or nonabsorbable sutures during fixation could adversely affect fertility by violating the blood-testis barrier and does not guarantee a future free of recurrent episodes of spermatic cord torsion.[110] As a result, placement of the preserved testicle into a dartos pouch without suture fixation is still a viable option.

TORSION OF VESTIGIAL APPENDAGES

The most common cause of testicular pain, torsion of a vestigial appendage, occurs primarily in boys between 2 to 12 years of age. With the acute scrotum, it comprises between 24% to 46% of cases.[111,112] The vestigial appendages of the testicle are embryologic remnants of the müllerian or wolffian duct (Fig. 42-22).

The appendix testis, or hydatid of Morgani, is an anatomic vestige of the müllerian duct. This pendulous structure lies within the tunica vaginalis and arises from the superior poles of the testis. It is found in 90% of males, and bilaterally in 60%. The other appendices infrequently are reported as culprits in the etiology of the acute scrotum. Approximately 91% to 95% of twisted testicular appendices involve the appendix testes. Symptoms mimic those of testicular torsion but are insidious in onset and less severe. There is often an associated localized upper pole hydrocele and an inflammatory reaction in the epididymis, which is often enlarged.[111] The infarcted appendage is visible and palpable in up to 21% of patients ("blue-dot" sign).[112] Often the entire testis is mildly tender, and the cremasteric reflex should be intact.

Sonographic evaluation of torsion of the appendages of the testes usually reveals a circular mass with variable echogenicity adjacent to the testis or epididymis. A reactive hydrocele may also be present and may help with the ultrasound diagnosis, because the appendage may be seen in the fluid of the hydrocele. Increased peripheral flow may be seen around the torsed appendage on color Doppler ultrasound, with normal flow to the ipsilateral testis. If the diagnosis is certain, bed rest and analgesia with oral nonsteroidal anti-inflammatory drugs are sufficient. The pain usually resolves in 5 to 10 days. If the findings at the time of initial evaluation are equivocal, immediate exploration is indicated.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP) is a rare cause of acute, painful groin swelling. It is characterized by nonthrombocytopenic purpura and is the most common systemic vasculitis of unknown origin diagnosed in children. It is usually accompanied by a palpable skin rash, colicky abdominal pain, and arthralgia, and it sometimes involves the kidneys, leading to nephritis and hematuria.[113] It occurs in approximately 3% of all cases of acute scrotum,[114] and between 2% to 38% of children with HSP experience scrotal involvement. The symptoms of involvement of the external genitalia are painful swelling and ecchymosis. The most commonly involved sites are the scrotal wall, epididymis, testis, testicular appendage, and spermatic cord, but the glans and shaft of the penis can also be involved.[115] In general, scrotal symptoms of HSP seem milder than those observed in testicular torsion. In some cases, sudden onset of acute scrotal pain may be the initial manifestation of the disease, preceding the systemic symptomatology by several days.

HSP occurs within the first 2 decades of life.[116] Histopathologically, HSP is characterized by vascular deposits of immunoglobulin A–dominant immune complex.[117] HSP is self-limited and is responsive to steroid therapy. Most cases resolve within 1 month, although the opposite side may become involved. Although scrotal exploration is unnecessary, many patients undergo exploration in this setting because of the clinical suspicion of testicular torsion. Scrotal scintigraphy and color Doppler sonography are quite reliable in documenting normal blood flow in these patients. Expectant management should be followed if the study shows either normal or increased perfusion.

Trauma

Blunt scrotal trauma can cause significant injury which, if not correctly diagnosed and treated, may result in loss of the testicle.[118] The testicle may suffer a hematoma or contusion, rupture of the tunica albuginea, traumatic dislocation from the scrotum, hematocele, or delayed hydrocele or pyocele.[119] The cause is usually a direct blow to the testicle in a sports-related injury, motor vehicle accident, or violent assault.

Patients present with post-traumatic pain, variable swelling, and scrotal ecchymosis which may extend into the penis. In a series of 65 patients presenting with scrotal trauma, ultrasound was shown to have excellent sensitivity (100%) and specificity (94%) in diagnosing testicular rupture[120] (Fig. 42-23).

If a rupture is present, it should be repaired surgically to prevent secondary infection, abscess, and eventual atrophy with loss of spermatogenesis. Cass and Luxenberg[121] reported a 20-year experience comparing primary conservative management (before 1971) with the new and now standard approach of early operative exploration and repair. They found a 45% orchiectomy rate in the delayed surgical intervention group, versus a 9% rate in the early surgical exploration group (defined as within 3 days after the injury). Any compromise to the testicular blood supply should also lead to surgical exploration.

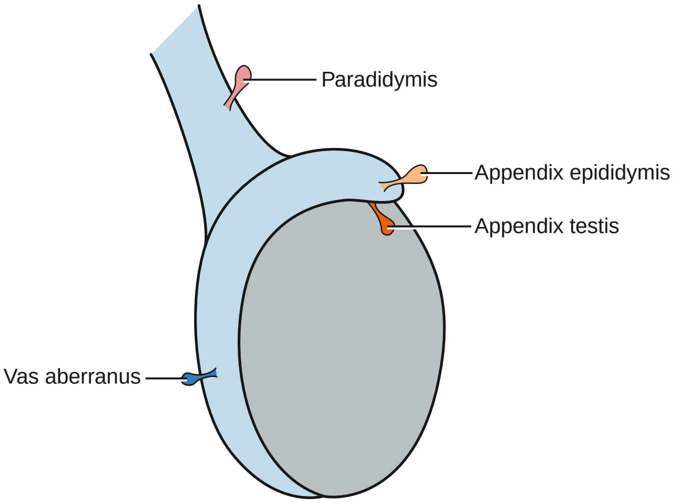

Figure 42-22 The vestigial appendages. (From Sidhu PS. Clinical and imaging features of testicular torsion: role of ultrasound. *Clin Radiol.* 1999;54:343-352.)

Varicocele

A varicocele is an abnormal dilation and tortuosity of the pampiniform plexus within the spermatic cord. Varicoceles are usually left-sided and rarely bilateral.[122] Although most varicoceles are asymptomatic, some boys experience significant testicular pain, particularly during exercise. Patients with intratesticular varicocele may have pain related to passive congestion of the testis, which eventually stretches the tunica albuginea.[123]

The physical examination is usually sufficient to diagnose a varicocele. Classically, palpation of the scrotum reveals "a bag of worms." The mass of veins disappears when the child lies down, but transmission of pressure through the plexus may be perceived with a Valsalva maneuver.[124] Treatment is usually unnecessary unless the child has testicular pain or shows testicular atrophy, in which case varicocelectomy is indicated.[125]

Inflammatory Causes

EPIDIDYMITIS

The exact incidence of epididymitis is unknown but has been estimated to range from 28% to 64% of acute scrotum cases.[126] The onset of pain associated with epididymitis typically is more gradual than of torsion of the testis, and fever and irritative urinary symptoms are more common. The peak incidence of epididymitis is between 9 and 14 years of age.[127] Epididymitis in younger males and infants has been correlated with anorectal[128] and genitourinary malformations.[129] As a result, its presence in prepubescent males should prompt an evaluation for congenital anomalies. The etiology and management of epididymitis are still subject to controversy. Several causes have been proposed, including ascending infection, urethrovasal reflux, nonbacterial inflammation, and amiodarone use.[130] There is also a recent report suggesting a postinfectious etiology with elevated viral titers compared to controls.[131] Bacteriuria is relatively uncommon, representing only 15.8% of cases.[132]

The physical examination varies from slight scrotal swelling to marked edema, intense pain, fever, and pyuria.[132] Color

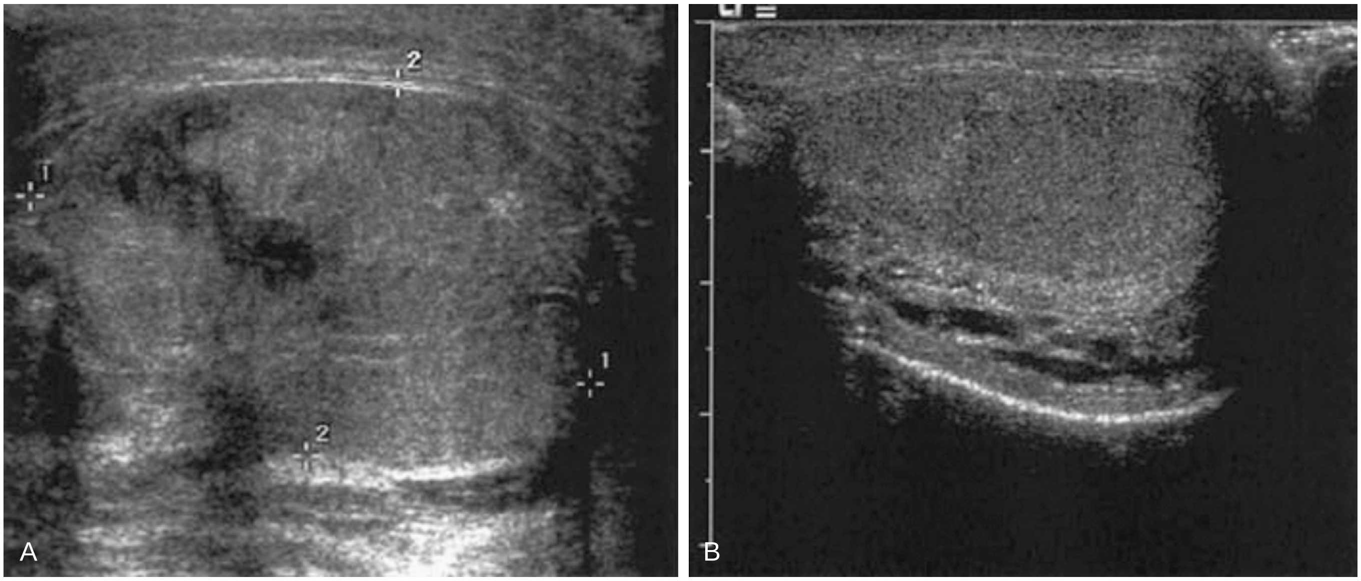

Figure 42-23 Scrotal ultrasonography of blunt testicular rupture. **A,** Preoperative view. Note heterogeneous echo pattern of testicular parenchyma. **B,** Postoperative view. Note excellent preservation of parenchyma with homogeneous appearance. (From Caldamone AA, Valvo JR, Altebarmakian VK, Rabinowitz R. Acute scrotal swelling in children. *J Pediatr Surg.* 1984;19:581-584.)

Doppler ultrasonography shows hyperemia of the epididymis with a diagnostic sensitivity approaching 100%.[133,134] Equivocal findings warrant surgical exploration.[97] For boys with acute epididymitis who have no urinary tract anomalies, no pyuria, and no positive urine culture, antibiotics are not indicated.[135] Systemic and local signs and symptoms resolve gradually in 1 to 7 days.

HYDROCELE

Fluid between the parietal and visceral layers of the tunica vaginalis forms a hydrocele. Normally, the processus vaginalis is obliterated in utero; if it does not obliterate, fluid can pass between the scrotum and the peritoneal cavity *(communicating hydrocele)*. A hydrocele may manifest as chronic or sudden swelling of the scrotum without pain or tenderness. A hydrocele may also develop acutely after testicular torsion, torsion of the appendix, testis epididymitis, or trauma.

Physical examination shows a tense scrotum that may have a bluish hue but is rarely tender. Hydroceles may exhibit diurnal variation in size, being larger in the evening, after the child has been upright all day. The majority of hydroceles transilluminate, but bowel fluid and air transmit light similarly to hydrocele fluid. Hematoceles may also manifest as acute scrotum but are usually the sequelae of blunt abdominal trauma.[136] Meconium-filled hydrocele sacs can cause acute scrotum in newborns.[137] There have been rare reports of torsion of communicating hydroceles.[138] High ligation of the hydrocele through an inguinal incision is curative, but diagnosis can be difficult. Sonographic imaging may not clearly diagnose this phenomenon[139] (Fig. 42-24).

INGUINAL HERNIA

Indirect inguinal hernia is the protrusion of an abdominal organ into a patent processus vaginalis extending into the inguinal canal. A hernia in a child is seldom symptomatic unless it is incarcerated. Physical examination may reveal a reducible, firm bulge in the groin and scrotum. Incarceration of the hernia sac and its contents occurs when the contents become stuck beyond the internal ring; this tends to occur in younger patients. Prompt reduction is required; otherwise, strangulation will occur secondary to intestinal swelling and impairment of blood supply.

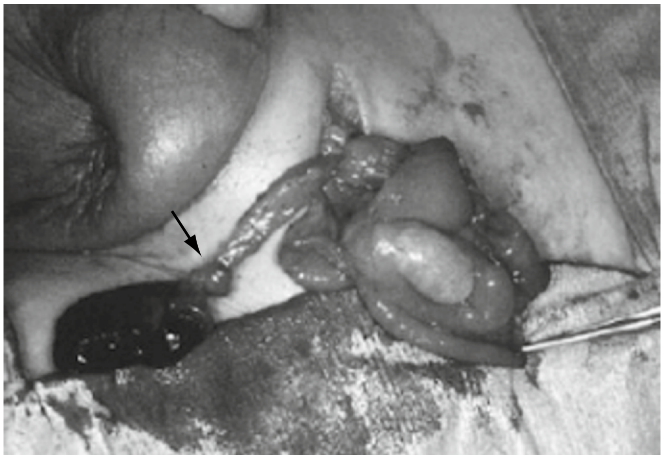

Figure 42-24 Intraoperative photograph of detorsed hydrocele. Clockwise rotation of 360 degrees was observed, and the hemorrhagic cystic mass led to tunica vaginalis. (From Anderson PA, Giacomantonio JM, Schwarz RD. Acute scrotal pain in children: prospective study of diagnosis and management. *Can J Surg.* 1989;32:29-32.)

An incarcerated hernia should be suspected in a patient who presents with severe, sudden onset of pain and a hard, tender, fixed mass in the groin. Intestinal obstruction may cause symptoms associated with bowel obstruction, and these patients typically appear acutely ill. Blood supply to the testicle may be impaired by an incarcerated hernia due to swelling of the hernia sac that impinges on the spermatic vessels.[140] Reduction of an incarcerated hernia should be attempted with proper narcotic analgesia and monitoring. Surgical exploration is mandated if manual reduction is not successful. Six cases of torsion of an indirect hernia sac have been reported.[141] The presentation is usually acute but with less severity compared to testicular torsion.

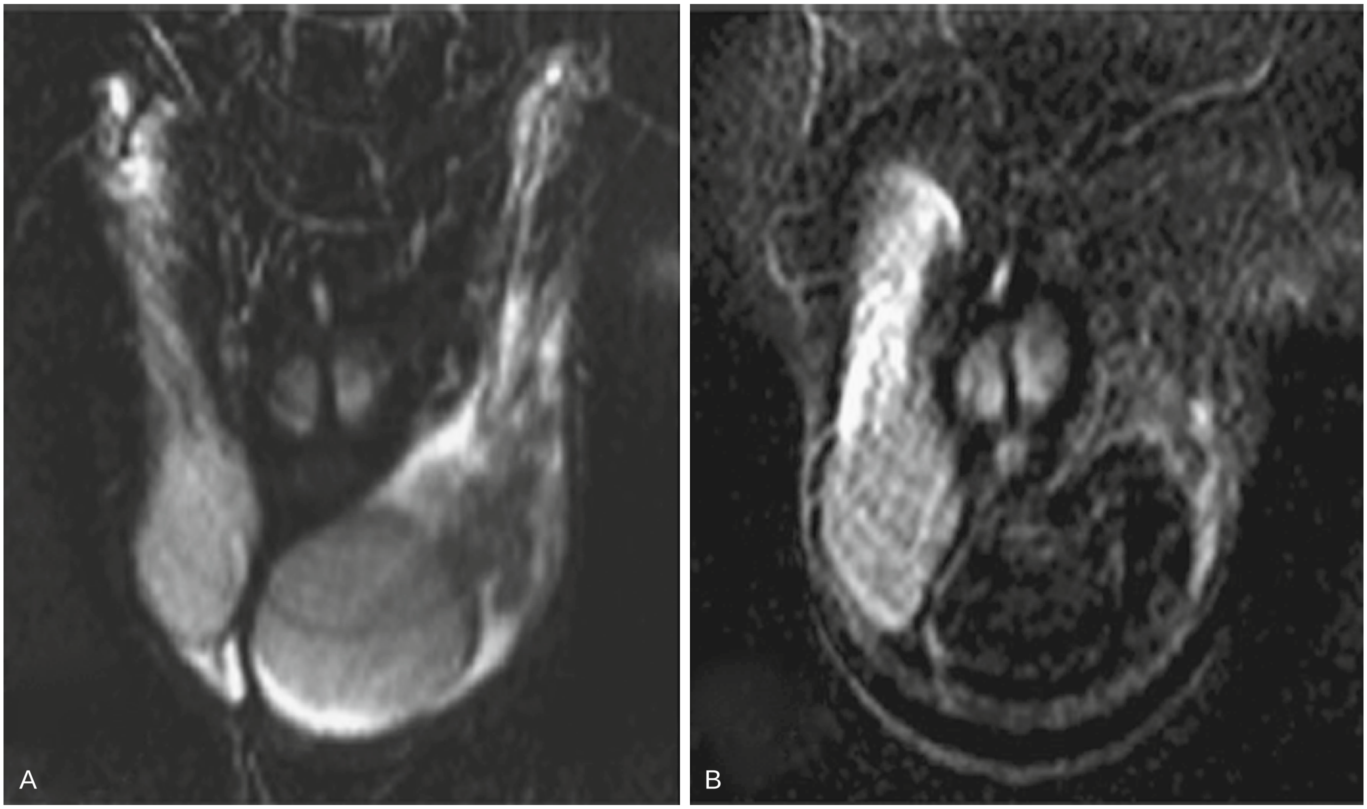

Figure 42-25 Examination performed 2 hours after onset of left scrotal pain. **A,** T2-weighted magnetic resonance image (MRI) shows slightly low signal intensity of left testis. **B,** On dynamic subtraction MRI, the left testis showed no contrast enhancement. (From Ameh EA. Morbidity and mortality of inguinal hernia in the newborn. *Niger Postgrad Med J.* 2002;9:233-234.)

Imaging Techniques

Ultrasonography

Scrotal ultrasonography is essential for the evaluation of scrotal and testicular pathology. It is performed with the patient lying in a supine position and the scrotum supported by a towel placed between the thighs. Color and power Doppler techniques have obvious advantages over gray-scale sonography, allowing early diagnosis to the extent that they highlight perfusion changes from the very beginning.[142] It is possible to detect the absence of blood flow in the symptomatic testicle, whereas flow is normally present in the contralateral testis. Major limitations to color Doppler include the required technical skill of the sonographer and difficulty in assessing blood flow in some boys younger than 13 years old. Ingram and Hollman noted that 38% of normal boys aged 10 weeks to 13 years had no flow detectable with color Doppler ultrasound.[143] Diagnosis can also be problematic with partial or incomplete torsion or with rotation of less than 360 degrees in which there is complete obstruction of venous flow, although arterial flow is still detected. In these cases, spectral analysis shows an increase in the resistive index with inversion of diastolic flow.

Testicular Scintigraphy

The goal of radionuclide scintigraphy is to distinguish torsion, with reduced or absent flow, from an inflammatory condition. Scintigraphy lacks anatomic detail, so subtle anatomic changes within the testicle or epididymis may not be visualized. It can be difficult to distinguish among acute torsion, hydrocele, and testicular or scrotal abscess.[144]

Spontaneous detorsion may yield a false-negative result.[145] In a prospective study comparing color Doppler sonography with scintigraphy in 46 children with acute scrotal pain, both modalities had similar sensitivity (79%) and specificity (90% to 97%). The authors concluded that a small number of false-negative cases can occur with either modality, but either may provide complementary information in indeterminate cases. Scintigraphy may not be available at all times, limiting its common use today in the workup of acute scrotum.

Magnetic Resonance Imaging

MRI can provide information about testicular perfusion because of its high sensitivity for contrast enhancement. The sensitivity was reported to be 93%, with a specificity of 100%, in 39 patients in whom the combined physical examination and ultrasound findings were deemed inconclusive.[146] This technology can overcome the limitations of operator variability seen with ultrasound. However, the increased cost and the lack of a 24-hour standby MRI limit its clinical utility (Fig. 42-25).

Medicolegal Aspects

Testicular torsion is a potentially active area in litigation because of the urgency in diagnosis, the diagnostic uncertainty, the potential adverse outcome, and the psychological impact related to loss of a testis.[147] However, these cases represent a minority of claims made against urologists, compared to urologic oncology and female urology.[148] A retrospective study of more than 50% of insured physicians in New Jersey reported a total of 39 cases over 18 years. Most of these were settled with a mean payment of $60,000. The most common misdiagnosis was epididymitis or epididymo-orchitis. Urologists were most frequently faulted for failure to order a radiologic study, although four paid claims were related to surgical misadventure. Risk factors for litigation included atypical presentation and older age.

REFERENCES

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CHAPTER 43

CRYPTORCHIDISM

Berk Burgu, Linda A. Baker, and Steven G. Docimo

Cryptorchidism (from the Greek *kryptos,* meaning "hidden," and *orchis,* meaning "testis") refers to absence of a testis from the scrotum. During embryonic life, the testes form beside the mesonephric kidneys and descend via the inguinal canal to the scrotum. If this process is faulty, a cryptorchid testis may halt along the normal path of descent (undescended or retractile testis), may travel off the normal path of decent (ectopic testis), or may die or never develop (absent testis). Therefore, the terms "cryptorchid" and "undescended" are not synonymous.

Isolated cryptorchidism is the most common congenital anomaly of the male genitalia, affecting almost 1% of full-term infants at the age of 1 year.[1] Despite intense study both experimentally and clinically for the last century, the cause of this condition remains poorly understood. Although there have been surgical advances in the techniques of orchiopexy, areas of clinical controversy remain.

OVERVIEW OF MALE SEXUAL DEVELOPMENT

In mammals, sexual determination, wherein the undifferentiated gonad converts to either a testis or an ovary, is genetically determined. The molecular basis of testicular determination is better understood than that of ovarian determination. Sexual differentiation, wherein the internal and external genitalia differentiate as appropriate to the gonadal sex, is dependent on hormonal function of the differentiated gonad. Therefore, the normal male and female phenotypes are the result of cascades of gene activations and hormone-receptor interactions that are tightly regulated temporally and spatially in the developing embryo.

In the 5th week of human gestation, the coelomic epithelium and underlying mesenchyme proliferate medial to the mesonephros, producing the bipotential gonad with a cortex and medulla. This process is dependent on such genes as the Wilms' tumor gene *(WT1)* and steroidogenic factor 1 *(SF1)*.[2] In week 6, under the activation of the *SRY* (sex-determining *r*egion *Y*-linked) gene on the short arm of the Y chromosome and other downstream testis-determining genes including *SOX9, FGF9,* and *DAX1*,[2] the cortex regresses and medullary testicular cords develop. In week 6, primordial germ cells in the yolk sac wall migrate along the hindgut dorsal mesentery and populate the gonad. Sertoli cells, producing anti-müllerian hormone (AMH), appear by week 6 and Leydig cells, producing testosterone and insulin-like factor 3 (INSL3), appear by week 8.

To achieve the normal male phenotype (including male internal and external reproductive organs and male secondary sex characteristics), these hormones require normal hormone and receptor function, quantity, location, and timing. In the absence of these critical testicular hormone interactions, female sex differentiation (or abnormal male sex differentiation) ensues. Each hormone has a strong ipsilateral paracrine effect. Internally, AMH causes involution of the müllerian duct, INSL3 causes masculinizing outgrowth of the male gubernaculum, and testosterone masculinizes the wolffian duct and causes male gubernacular regression. In weeks 10 to 15, male external genital development requires the conversion of testosterone to dihydrotestosterone by the enzyme 5α-reductase type 2 in these tissues. Proper scrotal development enables the testis to reside in an extracorporeal position.

TESTICULAR DESCENT

Testicular descent is necessary for normal spermatogenesis, which requires the 2° C to 3° C cooler scrotal environment. Embryonic testicular descent can be divided into three phases:

1. Transabdominal migration of the testis to the internal inguinal ring
2. Development of the processus vaginalis and the inguinal canal
3. Transinguinal descent of the testis to the scrotum

Transabdominal Migration

During the 6th gestational week, the testis is located ventromedial to the mesonephros, relatively close to the inguinal region. As the fetus and abdominal cavity enlarge, the testis remains relatively stationary, whereas the ovary ascends. To achieve this differential movement, the key structure in humans is the gubernaculum (or caudal genital ligament). Before gonadal differentiation, the male and female gubernaculum is a short, thin ligament extending from the lower pole of the undifferentiated gonad and its duct to the genital swellings, the precursors of the male scrotum and female labia majora. After testis formation, the male gubernaculum masculinizes via outgrowth, with mesenchymal proliferation and increased hyaluronic acid content, anchoring the testis. In females, the gubernaculum remains thin and lengthens in proportion to fetal growth, allowing ascent. This sexually dimorphic outgrowth of the mesenchymal gubernacular cone in males, the hallmark event during the male transabdominal phase, is not dependent on androgens[3] but is stimulated by the testis hormone, INSL3 (also known as Leydig insulin-like hormone or relaxin-like hormone) (see later discussion).

Because rodent models are frequently used to study testicular descent, it is noteworthy that, in these animals, the testis and ovary are suspended to the abdominal wall by a second ligament, the cranial gonadal suspensory ligament. In male rodents, testosterone stimulates cranial gonadal suspensory ligament regression, thereby permitting caudal testicular mobility. In females, this ligament persists due to the absence of testosterone, and caudal ovarian mobility is thus prevented.[4] The cranial gonadal suspensory ligament is present but becomes vestigial in humans.

In summary, INSL3 causes the early masculinizing gubernacular swelling reaction in males, and androgen causes regression of the cranial suspensory ligament (in mice). The coordinated result of masculinization of the gubernaculum during transabdominal migration in humans is positioning of the testicle at the internal inguinal ring by the 12th week of gestation.

Processus Vaginalis

In gestational month 3, an elongated pocket of peritoneum, called the processus vaginalis, grows along and partially encircles the gubernaculum, creating a potential space in the inguinal canal and scrotum. Although the testis is stationary between the 3rd and 7th months of fetal life, the gubernaculum and the processus vaginalis together distend the inguinal canal and scrotum,[5] creating a "path" for testicular descent.

Transinguinal Descent

This final phase of testicular descent occurs very rapidly, usually between weeks 24 and 35 of gestation.[6] During this time, testosterone shrinks the enlarged, masculinized gubernaculum by decreasing its turgidity and viscoelastic properties, yielding the gubernacular ligament.[3] Normally, the processus vaginalis obliterates completely before birth, but if the testis does not descend, the processus vaginalis usually remains patent, resulting in an open internal ring to the inguinal canal.

About two thirds of cryptorchid neonates have spontaneous postnatal testicular descent, typically within 6 months.[7] If the testis is undescended at birth, descent is presumably caused by the burst of testosterone (mini-puberty) that occurs during the first 3 months postnatally,[8] secondary to activation of the hypothalamic-pituitary axis by loss of negative feedback from the maternal endocrine environment. Some data suggest that the postnatal rise in serum testosterone is lower in boys with cryptorchidism than in those with normal testicular descent, possibly because of a primary deficiency in pituitary secretion of luteinizing hormone (LH).[9] However, Barthold and colleagues recently reported conflicting data showing no significant hormonal differences between these groups.[10]

FACTORS IN TESTICULAR DESCENT

The observation by John Hunter[11] that the testis might fail to descend because it is intrinsically abnormal—rather than being abnormal because it fails to descend—remains a focus of investigation and debate. Several different animal models have been used to study testicular descent, but they add to the controversy because of the differing anatomic structures in different species, including the cranial gonadal ligament, gubernaculum, and cremasteric muscles. Although animal models may not exactly represent testicular descent in man, much useful information has been gained from studies of hormonal and mechanical factors.

Hormonal Factors

Key hormonal factors implicated in testicular descent include the androgens, INSL3, estrogens, and AMH.

Androgens and the Androgen Receptor

In 1931, Engle suggested that an intact hypothalamic-pituitary-testis axis is essential for normal testicular descent[12]; this is supported by clinical evidence. Boys born with hypogonadism or androgen insensitivity are likely to be affected with cryptorchidism. Complete androgen insensitivity syndrome (CAIS), caused by an androgen receptor mutation, is associated with bilateral cryptorchidism in most cases and with intra-abdominal location in 52%.[13] However, androgen insensitivity is associated with a complete female phenotype or male pseudohermaphroditism, which is not observed in most cases of human cryptorchidism. Similarly, anti-androgens prevent testicular descent (by blocking gubernacular regression) in 50% of prenatally exposed rodent and porcine models.[14,15] Lastly, prenatal exposure of rodents to estrogenic compounds induces cryptorchidism, and this effect can be overcome by simultaneous treatment with dihydrotestosterone or human chorionic gonadotropin (hCG). These observations support the role of androgens in descent. However, the variability in testicular position among children with abnormal androgen actions and the partial success of anti-androgen–induced cryptorchidism in animal models shed a negative light. In addition, this clinical situation and this animal model are both associated with genital ambiguity. Prenatal estrogenic exposure can induce partial persistence of the müllerian structures. However, most children with cryptorchidism have unilateral disease, no genital ambiguity, and no persistence of the müllerian structures. In summary, these clinical and experimental observations suggest a partial role of androgens in testicular descent.

Insulin-like Factor 3 and Its Receptor

For more than 30 years, it has been recognized that (1) exogenous androgens are unable to stimulate outgrowth of the gubernaculum in female fetuses, (2) anti-androgens fail to block outgrowth of the gubernaculum in male fetuses, and (3) gubernacular outgrowth is normal in humans or animals with testicular feminization.[16] In contrast, androgenic stimulation clearly induces the regression phase of the gubernaculum after the initial outgrowth phase. These observations and animal experiments in which fetal orchiectomy induced failure of gubernacular growth led to the theory of "descendin,"[17] a testicular hormone with specific local effect on gubernacular cell growth. In 1993, this hormone, now called INSL3, was first discovered. Its function was identified in 1999, when INSL3-knockout mice[18,19] were found to have bilateral intra-abdominal undescended testes due to absent gubernacular outgrowth phase yet had normal androgenization of the other male internal and external genitalia.

INSL3 is produced by the fetal testis and not by the fetal ovary. The gubernaculum, which expresses the INSL3 receptor, LGR8, is stimulated to outgrow in males by INSL3; females do not make INSL3 during fetal life. Therefore, INSL3 and its receptor, LGR8 (a member of the G protein–coupled receptor family, sometimes called GREAT), are the critical regulators of the transabdominal phase of masculinizing gubernacular outgrowth. Approximately 2% of patients with isolated cryptorchidism have functionally deleterious mutations in the INSL3 or LGR8 gene, but further study is needed to identify other regulators of the INSL3 signaling pathway in humans.

Estrogens

Several studies have suggested that human maternal estrogens may modulate testicular descent. Gill and associates noted an increased incidence of cryptorchidism in the male offspring of women treated during pregnancy with diethylstilbestrol (DES), a nonsteroidal estrogenic compound.[20] In addition, Bernstein and colleagues[21] observed that male infants born to mothers with high levels of free estradiol had a higher frequency of cryptorchidism. Evidence indicates that there may be an increased expression of estradiol in the placenta of boys born with undescended testes.[22] In support, one method to generate rodent male offspring with cryptorchidism is through prenatal estrogen exposure[23,24]; and more recent mouse work has shown that estrogens ablate INSL3 messenger RNA expression, accounting for the cryptorchidism.[25] Of note, this experimental model also induces retention of müllerian structures to some degree.

Anti-müllerian-Inhibiting Substance

The observation that patients deficient in AMH (also called müllerian inhibiting substance, or MIS) typically have intra-abdominal testicles led to the suggestion that AMH may play a role in testicular descent.[26] However, AMH deficiency in humans probably prevents testicular descent indirectly, through the obstruction produced by the persistent müllerian structures, rather than by a direct lack of hormone.[27,28] In addition, most males with intra-abdominal cryptorchid testes have no persistent müllerian structures. Other pieces of experimental evidence refute the role of AMH in testicular descent, including prenatal exposure to anti-AMH antibodies[29] and the phenotypes of AMH or AMH receptor knockout mice.[30]

Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide (CGRP) is a neuropeptide released from the genitofemoral nerve, which originates from the cremaster nucleus in the spinal cord. Evidence that the cremaster nucleus is sexually dimorphic and androgen dependent, and that its efferent neuron secretes a neuropeptide that can cause contraction of the rat gubernaculum, has implicated CGRP and the genitofemoral nerve as important factors in testicular descent. However, contrary evidence that masculinization of the cremasteric nucleus may not be androgen dependent[31] and that the gubernaculum of primates contains almost no muscle[6] suggests that CGRP may play only a minor role in this process in humans. *Hoxa10* mutant mice demonstrate cryptorchidism; the cause may be anterior homeotic transformation of L1 and L2 nerves with incorrect specification of genitofemoral nerve motoneurons or abnormal target tissue innervation or both.[32] Allelic variants in *HOXA10*[33] and *HOXD13*[34] have been reported in a few cryptorchid boys.

Epidermal Growth Factor

Epidermal growth factor (EGF) can cause persistence of the wolffian ducts in the absence of androgens,[35] and it has also been shown to act on the placenta and, secondarily, to increase testosterone production. In mice, maternal EGF appears to precede testosterone secretion by the fetal testis and may therefore play some role in testicular descent[36]; however, this has not been investigated in humans.

Mechanical Factors

First described and named by John Hunter in 1762,[37] the term *gubernaculum* means "helm" or "rudder," and this structure was thought to guide the testis into the scrotum. Perhaps the most important mechanical factor, the gubernaculum begins as a mesenchymal band that originates on the lower pole of the testis/mesonephric duct and inserts in the scrotum. Separate extrascrotal bands or "tails" were described by Lockwood,[38] which may explain the occurrence of testicular ectopia. Its morphogenesis includes an "outgrowth" phase mediated by INSL3 and a regression phase mediated by androgens, as detailed earlier. The exact mechanism through which the gubernaculum mediates testicular descent is debated and may involve traction, muscular contraction, or differential growth around a fixed point. Most likely, the gubernaculum, in conjunction with the processus vaginalis, serves to dilate the inguinal canal and thereby facilitate descent of the testis into the scrotum.[16]

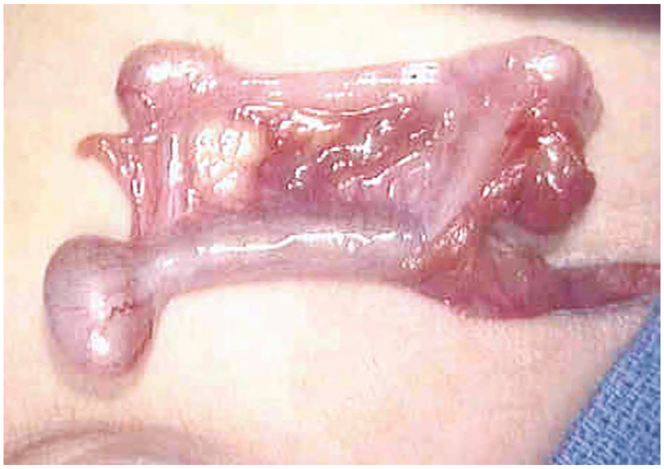

Figure 43-1 Significant epididymal dissociation in a left undescended testis at inguinal exploration.

In 1969, Gier and Marion proposed that intra-abdominal pressure may be responsible for testicular descent.[39] Clinically, males with prune-belly syndrome or other abdominal wall defects such as gastroschisis, omphalocele, or umbilical hernia[40] frequently have cryptorchidism. However, against this is evidence that intact abdominal wall musculature is not necessary for testicular descent.[41] The intra-abdominal pressure theory is also insufficient to explain unilateral cryptorchidism.

The role of the epididymis in testicular descent is based on the fact that it is androgen dependent, adjacent to the gubernaculum, and often abnormal in boys with cryptorchidism.[42] The epididymis precedes the testis into the scrotum but does not significantly enlarge until after scrotal positioning. Removal of the epididymis does not prevent testicular descent,[43] and congenital absence of the wolffian ducts does not impair testicular descent.[44] Therefore, it is unlikely that the epididymis plays a significant role in descent. Epididymal anomalies are seen adjacent to undescended testes in 33% of cases (Fig. 43-1), but they are five times more common in patients with an inguinal hernia than in patients with cryptorchidism,[45] suggesting that other factors may be involved.

DEFINITIONS AND CLASSIFICATION

Based on physical findings, cryptorchidism is classified as palpable testes in 80% of the cases, and as nonpalpable testes in 20%. Knowing the location and existence of the testis directly influences clinical management. *Palpable testes* include true undescended testes and ectopic testes; because retractile testes are often misdiagnosed as palpable undescended testes, they are also discussed in this category. *Nonpalpable testes* include intra-abdominal, inguinal, and absent testes.

Palpable Testes

Undescended Testis

A true *undescended testis* is a testis halted along its normal path of descent. Depending on its location, it may or may not be palpable. Inguinal testes are an excellent example because they have halted along the normal path of descent in the inguinal canal, but they may or may not be palpable. When viewed laparoscopically, "peeping" testes move in and out of the internal inguinal ring (Fig. 43-2). An "emergent" or "gliding"

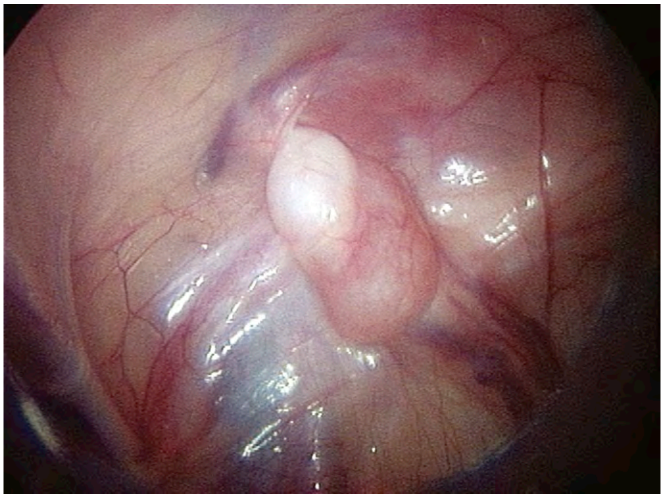

Figure 43-2 Intra-abdominal view of a “peeping” right nonpalpable testis. (From Baker LA, Lorenzo A, Jordan GH, Docimo SG. Laparoscopy and cryptorchidism. In: Docimo SG, ed. *Minimally Invasive Approaches to Pediatric Urology*. London: Taylor & Francis Publishers; 2005:161-176. Used by permission from Taylor & Francis.)

undescended testis moves in and out of the external inguinal ring, but because these terms have been confused with testes at the internal ring, they are best avoided. Higher testes are associated with foreshortened, fixed spermatic vessels; more wolffian duct anomalies; and a greater incidence of inguinal hernia.

Ectopic Testis

An *ectopic testis* is one that is located in an aberrant position off the path of normal descent (Fig. 43-3). The most common site of palpable ectopia is the superficial inguinal pouch of Denis-Browne, located between Scarpa’s fascia and the external oblique fascia above the external inguinal ring. Less common ectopic sites include the femoral, pubic, penopubic, penile, and perineal positions. In crossed or transverse ectopia, a testis crosses the scrotal septum or descends into the opposite inguinal canal. Nonpalpable ectopic sites include anterior abdominal wall, retrovesical, and other intra-abdominal positions. Ectopic descent is thought to result from overdevelopment of one segment of the gubernaculum (i.e., a tail of Lockwood) or from scrotal inlet obstruction. An ectopic testis is fixed in position by fibrous attachments and therefore cannot spontaneously descend; only surgery will correct this position.

Retractile Testis

A *retractile testis* is one that has completed the process of descent but may be found in the groin because of an overactive cremasteric reflex. The cremasteric reflex is a function of the genitofemoral nerve (L1) and is present in all boys older than 2 years of age.[46] When the reflex is elicited by tactile stimulation of the thigh, the cremaster muscle contracts and draws the testis out of the scrotum toward the inguinal canal. Teleologically, the cremaster reflex protects the testis by drawing it out of harm’s way, but it may cause a normal testis to mimic an undescended testis.

A retractile testis should be suspected in the 2- to 12-year-old child with a possible undescended testis. A retractile testis can be manipulated into the scrotum, where it will remain (at least temporarily) after its release. In contrast, the undescended testes retracts into the groin immediately. Retractile testes are typically normal in size and consistency, whereas undescended testes may be smaller and softer than normal.

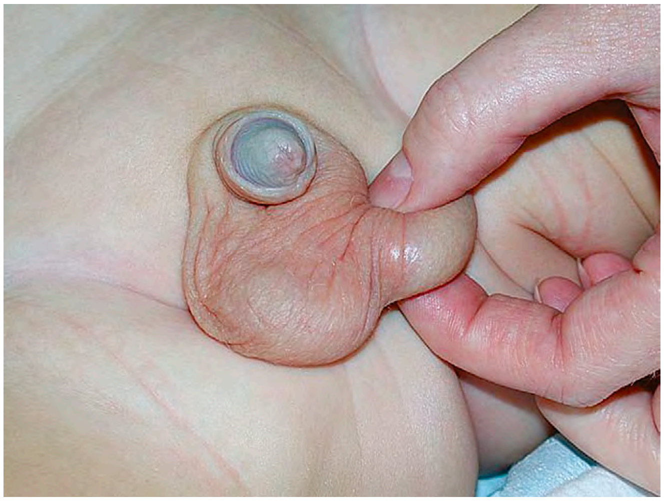

Figure 43-3 Empty left hemiscrotum with scrotal right testis. The left testis is located in a laterally ectopic position.

However, retractile testes may not be normal and should be annually monitored during childhood, because 30% descend, 38% remain retractile, and 32% ascend (become “undescended”).[47] At orchiopexy for an “undescended testis,” examination under anesthesia may reveal a scrotal testis, indicating that it is really retractile and obviating the need for surgery. However, orchiopexy via either an inguinal or a scrotal approach may still have merit under these circumstances, to prevent potential testicular ascent in the future.

Nonpalpable Testes

Approximately 20% of all cryptorchid testes are nonpalpable. Between 50% and 60% of these are intra-abdominal, canalicular (within the inguinal canal), or “peeping” (just inside the internal inguinal ring). Approximately 20% of nonpalpable testes (4% of all cryptorchid testes) are absent, and another 30% (6% of the total) are atrophic or rudimentary.

Intra-abdominal Testes

Intra-abdominal testes are located in a variety of intra-abdominal positions, the majority less than 2 cm from the internal ring. However, a testis can be adjacent to the kidney, on the anterior abdominal wall, retrovesical, and in other intra-abdominal positions. In rare cases, the wolffian ducts do not connect with the gonad (epididymal disjunction), leading to a large space between the cranial testis and the caudal epididymis/vas.

Intra-abdominal testes may be associated with a closed or an open internal ring. In the closed ring variant, the processus vaginalis does not develop, the gubernaculum is absent, and the internal inguinal ring is closed. This is the typical configuration seen with the prune-belly syndrome. In the open ring variant, a patent processus vaginalis exits the internal inguinal ring, and the gubernaculum is present. With the open ring variant, the testis may be “peeping” into the inguinal canal, depending on the length of the processus vaginalis and the testicular vessels.

Absent Testes

Although unilateral absence (monorchidism) occurs in 4% of patients with cryptorchidism, bilateral absence (anorchidism) occurs in fewer than 1%. Testicular agenesis and atrophy after intrauterine torsion are two mechanisms for testicular absence.

Table 43-1 Evaluation of Bilateral Nonpalpable Cryptorchidism

	Cryptorchidism	Anorchidism	Female Pseudohermaphroditism
Karyotype	46,XY	46,XY	46,XX
Serum testosterone			
Baseline	Normal	Low	Variable
hCG stimulation test	Positive	Negative	Negative
Gonadotropins	Normal	Increased	Normal
AMH/MIS	Positive	Negative	Negative
Adrenal steroid precursors	Normal	Normal	Increased
Ultrasonography			
Gonads	Testes or negative	Negative	Ovaries or negative
Internal ducts	Negative	Negative	Uterus/müllerian system
Genitogram	Male urethra	Male urethra	Urogenital sinus and/or müllerian structures
Laparoscopy			
Gonads	Testes	Blind-ending vessels	Ovaries
Internal ducts	Wolffian	Wolffian	Müllerian

AMH/MIS, anti-müllerian hormone/müllerian inhibiting substance; hCG, human chorionic gonadotropin.

VANISHING TESTIS

The term *vanishing testis* indicates that the testicular vessels and a vas deferens are found on surgical exploration, but a testis is absent. In utero infarction of a normal testis by gonadal vessel torsion after gestational weeks 12 to 14 is hypothesized, because ipsilateral wolffian duct differentiation and müllerian duct regression, both of which require ipsilateral testicular hormones, occur normally. Supporting evidence for testicular infarction includes the common finding of hemosiderin and calcium deposits in testicular remnants (“nubbins”) found on exploration.[48] Contralateral compensatory testicular hypertrophy, defined as a testis length of 1.8 cm or greater, has been found to be 90% accurate in predicting monorchia[49] but does not eliminate the need for surgical exploration.

In the evaluation and surgical treatment of nonpalpable testes, the presence of palpable ipsilateral scrotal appendages (i.e., tunica vaginalis, gubernaculum, or vas deferens) and a contralateral descended testis with no hypertrophy is associated with a 93% likelihood of discovering a testis that can be successfully relocated to the scrotum. Conversely, if the ipsilateral scrotal appendages cannot be palpated and the contralateral descended testis is hypertrophied, there is a 96% probability that the impalpable testis is vanished.[50]

TESTICULAR AGENESIS

Testicular agenesis may result from failure of the testicular blood supply to develop or from abnormal gonadal ridge differentiation. An example of the latter is 46,XY complete gonadal dysgenesis. However, these individuals are characterized by streak gonads, either female or ambiguous genitalia, and persistence of müllerian structures. The variable phenotypic appearance, including the presence and form of the external genitalia, relates to the time during gestation when the testis differentiation becomes abnormal. True congenital absence of a testis is extremely rare, and absence of both testes results in a female phenotype.

BILATERAL UNDESCENDED TESTES

At birth, approximately 1 of every 600 babies has bilateral undescended testes, representing 10% to 25% of patients with cryptorchidism. Because testicular descent is an event of the third trimester, this may be a common physical finding in premature male neonates. It is estimated that at least 6% of patients with bilateral undescended testes have an endocrine disorder as the cause.[51,52]

Bilateral undescended testes, if each testis is palpable, are managed in the same fashion as a unilateral palpable undescended testis. However, the finding of bilateral nonpalpable testes represents a special situation that can have life-threatening implications in the neonatal period, especially in association with hypospadias. The differential diagnosis of bilateral nonpalpable cryptorchidism includes anorchidism, undescended testes (bilateral or unilateral with contralateral absence), and ambiguous genitalia due to female pseudohermaphroditism or another intersex condition. It is this last possibility that necessitates an urgent and thorough evaluation to rule out life-threatening congenital adrenal hyperplasia (CAH). A karyotype, endocrine testing, radiographic studies, and, if indicated, laparoscopy usually provide the necessary information to make an intersex diagnosis (Table 43-1). A normal-appearing masculinized phallus with bilateral nonpalpable testes does not eliminate this possibility (Fig. 43-4). Routine neonatal screening for CAH has aided detection of this entity, but often these state-mandated test results are not available until 7 to 14 days after birth.

In the case in which an intersex disorder has been excluded, endocrine studies (hCG stimulation test, serum AMH level, or serum inhibin B level) may be useful to differentiate bilateral nonpalpable cryptorchidism from anorchia.[53] Administration of hCG can be used to stimulate testosterone production by testicular tissue, to detect its presence biochemically, and may also cause the gonads to become palpable by physical examination. However, false-negative hCG stimulation test

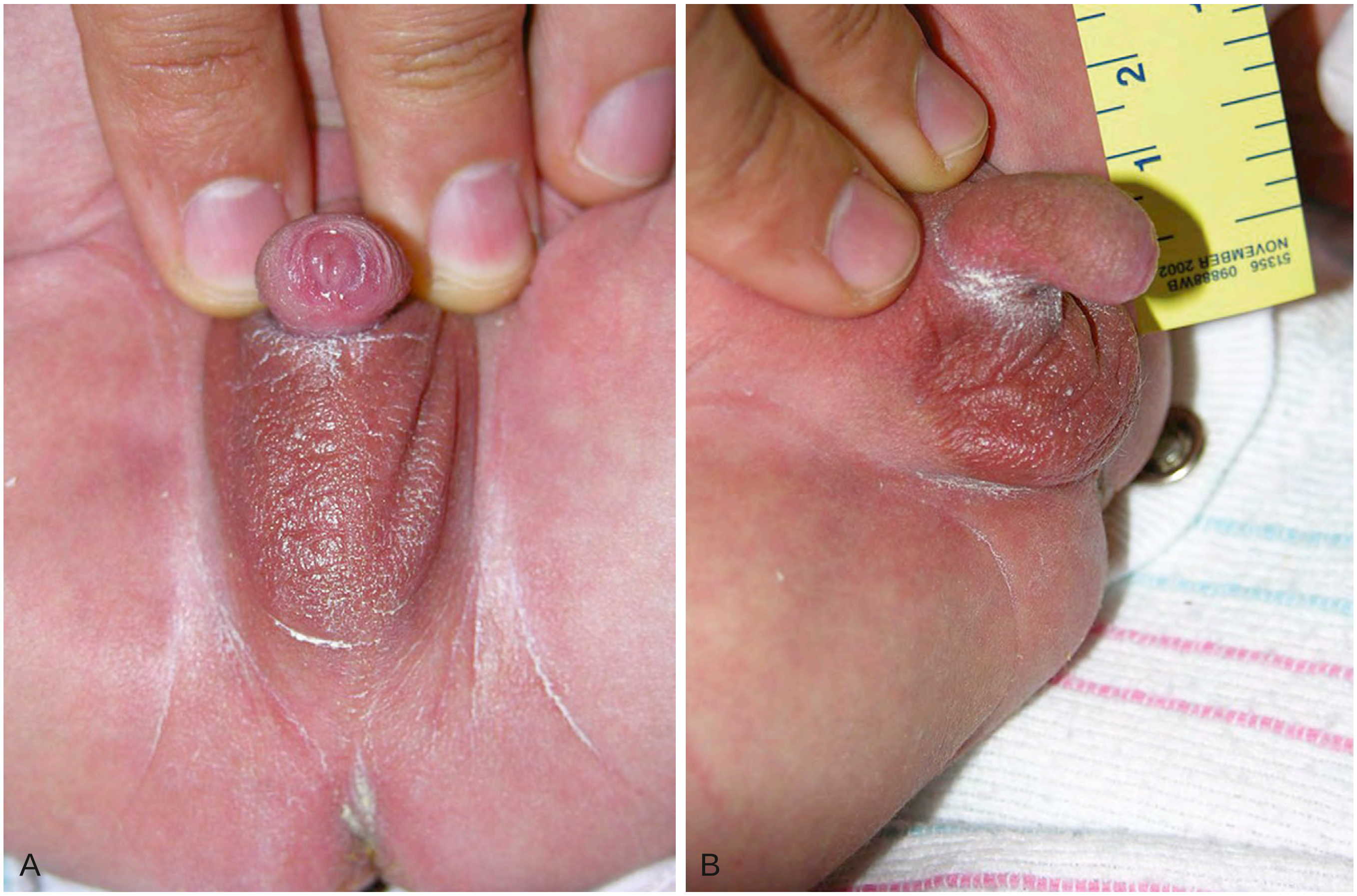

Figure 43-4 **A** and **B,** Newborn infant with bilaterally nonpalpable testis, normally formed scrotum, 3-cm phallus with mild chordee, and urethral meatus at the tip of the glans with complete foreskin. This child is a Prader 5 severely virilized 46,XX female with congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency.

results can occur if there is an unresponsive population of Leydig cells. Therefore, hCG stimulation testing is combined with the measurement of gonadotropins to diagnose anorchia. Markedly elevated gonadotropins before puberty are indicative of anorchidism,[53] but all boys with normal serum gonadotropin levels must undergo exploration regardless of the outcome of the hCG stimulation test.

Measurement of serum AMH can be used to provide additional evidence that testicular tissue is present, and recently this test has become widely available. In prepubertal cryptorchid children, the serum inhibin B level has been shown to negatively correlate with serum (basal or hCG-stimulated) levels of follicle-stimulating hormone (FSH)[54] and to positively correlate with the lack of testosterone response to hCG stimulation.[55] However, serum inhibin B levels can also be somewhat low in children with gonadal dysgenesis or a history of testicular trauma. If the clinical experience with serum AMH and serum inhibin B continues to show reliability, these tests may supplant the need for the hCG stimulation test. The determination of testosterone, its precursors, and dihydrotestosterone, after hCG stimulation, should be reserved for situations in which Leydig cell function needs to be specifically assessed.[56]

Therefore, in an infant with a male genotype, the diagnosis of anorchia can be made based on a low serum testosterone level, a negative hCG stimulation test, increased serum gonadotropins, a negative serum AMH result, a low basal serum inhibin B level, normal levels of adrenal steroid precursors, and radiographic studies demonstrating the absence of müllerian structures. In equivocal cases, diagnostic laparoscopy and/or open surgical exploration with gonadal biopsy may be required to confirm the diagnosis of anorchia (see Table 43-1).

TESTICULAR ASCENT

An *ascended testis* refers to a cryptorchid testis, usually one that is palpable, that was previously identified as descended in the scrotum. In the past, this was considered a misdiagnosis caused by an error in physical examination,[57] but the cumulative experience of qualified examiners suggests that it is a real phenomenon.[58] The risk of ascent may be as high as 32% to 50% in cases in which one testis is significantly retractile.[59,60] Ascended testes are typically unilateral (77%), identified in mid-childhood, and located distal to the inguinal canal (77%).[59] Ascended and significantly retractile testes may be prone to the same germ cell maldevelopment seen in congenital cryptorchidism.[59] Ascent is thought to be caused by relative shortening, or lack of elongation, of spermatic cord structures as the affected child grows.[61] The finding of a fibrous remnant within the spermatic cord, possibly an obliterated processus vaginalis, may limit cord growth.[62] Patients younger than 7 years of age who have tight, inelastic spermatic cords appear to be at highest risk for acquired cryptorchidism and should be examined annually until puberty.[60] Ascent may also be iatrogenic after an inguinal hernia repair.[63]

INCIDENCE AND NATURAL HISTORY

The incidence of cryptorchidism is age dependent, because testicular descent is completed during the third trimester of gestation. Approximately 33% of premature male infants are cryptorchid. The incidence in full-term males at birth is 2% to 4%, and at age 1 year it is 1%.[59] Most undescended testes that descend spontaneously do so during the first 3 months after term, and very few descend after that.[1,7] Unilateral cryptorchidism is more than twice as common as bilateral cryptorchidism (68% versus 32%, respectively), and the right side is affected more often than the left (70% versus 30%).

RISK FACTORS

Maternal, Paternal, and Gestational Factors

Maternal obesity, cesarean section, low birth weight, and prematurity have been associated with cryptorchidism, each independently doubling the relative risk over that of the general population.[64] In addition, shorter menses and later menarche were noted in mothers of cryptorchid boys versus controls.[65] Davies and colleagues noted an increased tendency toward threatened abortions, prior miscarriage, and decreased fertility.[66] These observations suggest that the maternal-placental-fetal hormonal state may be abnormal in affected individuals. Cryptorchidism was associated with paternal exposure to pesticides, which may indicate an effect on the paternal germline.[67] Race does not appear to be a significant risk factor.

Genetic Factors

Cryptorchidism frequently has strong familial clustering, and 14% of cryptorchid boys come from families in which other males are cryptorchid. Cryptorchidism is transmitted in a multifactorial pattern; fathers are affected with an incidence of approximately 4%, and siblings with an incidence of 6% to 10%. The increased incidence of cryptorchidism in first- and second-degree relatives warrants counseling and monitoring of families with cryptorchidism for its appearance in subsequent male children, including nephews and cousins. The frequency of sporadic and familial cryptorchidism suggests that genetic factors are involved.

With the recent increase in mutant mouse models of cryptorchidism, several investigators have performed candidate gene mutation screenings in cryptorchid patients. Mutations have been identified in the following genes: *INSL3*,[68-70] *LGR8*,[70,71] androgen receptor polymorphisms,[72] *HOXA10*,[33] and *HOXD13*.[34] Some of these mutations have been proved to be causal in cryptorchidism.

Environmental Factors

Some literature suggest that the incidence of cryptorchidism is increasing. One possible explanation is prenatal environmental exposure to a growing group of compounds termed *endocrine disruptors*. Such compounds include DES (synthetic estrogen), DDT (pesticide), nonylphenol (industrial surfactant), bisphenol-A and certain phthalates (plastics additives), and natural phytoestrogens (common in soy products).[73] These chemicals act as estrogen or androgen agonists or antagonists. Ample data from animal and human exposures demonstrate a causal relationship between such chemical exposures and cryptorchidism.[74] The necessary level of exposure (range of parts per billion) is probably very low, so exposure is commonplace. The future challenges lie in defining whether certain individuals are more susceptible, in delineating whether certain combinations of chemical exposures are more potent, and, ultimately, in effecting prevention of exposure.

ASSOCIATED ANOMALIES

Multiple factors are involved in normal testicular descent. As a result, many clinical syndromes that affect genetic integrity or the endocrine, musculoskeletal, and nervous systems can be associated with this condition. For example, abnormalities in chromosome number, such as autosomal trisomy, triploidy, and Klinefelter's syndrome (XXY), are commonly associated with cryptorchidism. Deficiencies in pituitary function, testosterone production, 5α-reductase activity, and androgen receptor sensitivity effectively interrupt androgen activity and can result in cryptorchidism. Infants with abdominal wall defects such as omphalocele, gastroschisis, or umbilical hernia, as well as prune-belly syndrome or bladder or cloacal exstrophy, often have undescended testes. Cryptorchidism is commonly present with an anomalous central nervous system, as in cerebral palsy, mental retardation, and spinal cord abnormalities. Overall, 15% of males with myelomeningocele are cryptorchid, with a 50% incidence among those affected above L4.

When hypospadias is accompanied by bilateral or unilateral cryptorchidism, a thorough investigation to exclude underlying genetic or endocrine abnormalities causing an intersex condition must be undertaken,[75,76] because disorders of sex development (DSD) are present in approximately 30% of these children. If the undescended testis is palpable, there is a 15% risk of intersex; if the undescended testis is nonpalpable, the risk is increased to 50%.[76]

Wolffian duct abnormalities have been reported in approximately 50% of those with undescended testes, including vasal and epididymal agenesis, segmental atresia, and elongation. Frank discontinuity may occur between the testis and epididymis. An elongated, or "long-looping," vas deferens is usually associated with an intra-abdominal testis but may also be seen with an inguinal testis. Patients with bilateral or nonpalpable undescended testes have a higher incidence of such anomalies, and the more proximal the location of the testis, the more severe the epididymal malformation.[77] Epididymal abnormalities are clinically important for three reasons. First, an abnormal vas deferens and epididymis may preclude the option of orchiopexy based on vasal and epididymal collateral blood supply. Second, in cases of disjunction between the testis and epididymis, epididymal tissue in the scrotum may be mistaken for an atrophic testis if surgical exploration is not performed. Third, epididymal anomalies may cause future infertility despite a technically successful orchiopexy.

DIAGNOSIS

History

Maternal and paternal prenatal risk factors, including hormone exposures, should be ascertained when evaluating a cryptorchid newborn. A family history of cryptorchidism or genetic or hormonal disorders might suggest further evaluation. In an older child, a history of previously descended testes suggests testicular ascent[57,58,78] and should not prompt criticism of previous examinations. A history of prior inguinal surgery suggests secondary cryptorchidism, though occasionally an inguinal hernia has been repaired without orchiopexy in an infant with an undescended testis, with the erroneous thought that the testis will descend spontaneously.

In adults with undescended testis, a fertility history may be pertinent.

Physical Examination

A general physical examination is carried out, and any abnormalities are noted. If a testis is not in the scrotum, the cryptorchid testis is sought by gently advancing the examining fingers along the inguinal canal toward the pubic tubercle. This examination is best facilitated by applying lubricant to the groin. The inguinal testis will be felt to "pop" under the fingers. The child may be examined in sitting or squatting position, which occasionally results in identification of a palpable testis that was not palpable in the supine position. If the testis is not found in the inguinal canal, all ectopic sites should be thoroughly examined. Some testes that seem retractile at a young age actually are ectopically attached testes that will ascend with linear growth.[57] Differentiating the true undescended testis from a retractile testis can be challenging, and a second examination in the office is often quite helpful. With experience, these can be delineated, prompting close observation or surgical repair, depending on the certainty of the diagnosis. Nevertheless, in some cases of retractile testes, the diagnosis is confirmed only after examination with the child under anesthesia.

If bilateral nonpalpable cryptorchidism exists, any evidence of intersexuality, including genital ambiguity and scrotal hyperpigmentation, should prompt further evaluation. In cases of unilateral or bilateral cryptorchidism, hypospadias may be a sign of an intersex condition.[75,76] In cases of unilateral nonpalpable cryptorchidism, the contralateral descended testis is examined. Any enlargement may suggest testicular absence or atrophy, although this sign is not specific enough to preclude surgical exploration.

Localization Studies

If a testis is not palpable, radiographic studies are often employed to localize and assess the presence or absence of a testis. Frequently, cryptorchid patients are referred to the pediatric urologist after an ultrasound study has been obtained. Elder found that 66% of ultrasound studies performed were unnecessary, because he was able to palpate the testis in question during the office visit.[79] Radiographic localizing studies cannot determine with certainty that a testis does not exist, and they cannot rule out the presence of an intra-abdominal testis.[80] Therefore, laparoscopy is the diagnostic procedure of choice for the nonpalpable testis because of its superior accuracy compared to other modalities.[81-83] However, radiographic imaging studies may be useful in certain clinical circumstances, such as the overweight boy with a nonpalpable inguinal testis and in follow-up of cryptorchid boys who, because of comorbid conditions, are not surgical candidates.

TREATMENT OF CRYPTORCHIDISM

Age

Therapy for cryptorchidism is usually carried out between 6 months and 1 year of age. Histologic deterioration of the cryptorchid testis has been noted as early as 12 to 18 months. Because testes rarely descend after 6 months,[7] there may be surgical advantages to orchiopexy within the first 6 months, especially in patients with high undescended testis. Decisions regarding orchiopexy after 1 year of age are based on the benefit of the testis to the individual. Although an undescended testis may function poorly for fertility, the usefulness in terms of androgen production must be considered, especially in cases of a solitary testis.

In some cases, a testis is found to be cryptorchid in an adult. Care of the postpubertal unilateral cryptorchid testis depends on the testicular size, ease of placement into the scrotum and health comorbidities. In 2002, a reassessment of the surgical and anesthetic risks and benefits in management of a postpubertal cryptorchid testis was published. For American Society of Anesthesiologists (ASA) class I or II cases, the anesthetic and surgical mortality risk of orchiectomy was greater than the risk of mortality from testicular germ cell malignancy after 50 years of age, and therefore the recommendation was for orchiectomy up until age 50 years.[84] For some patients with comorbid conditions, the risks of surgery may be significant even before this age is reached.

Indications

The four commonly cited indications to treat cryptorchidism are reduced fertility, testicular cancer, inguinal hernia, and testicular torsion.

Fertility

At birth and into the first year of life, undescended testes have normal histology, including a normal population of germ cells. Beyond 18 months of age, both light and electron microscopy demonstrate histologic changes suggesting deterioration of the germ cell population of the testis.[85,86] Such histologic changes can also be seen in a contralateral, descended testis after 2 years, suggesting that both the undescended and the scrotal testes can be intrinsically abnormal.[86] Grossly, this deterioration may result in testes that are smaller and softer than normal. Retractile testes are believed to be intrinsically normal, although there has been some debate on this point, possibly because of varying definitions of the term "retractile" and the selection of patients with infertility for adult testicular biopsy, which introduces bias.[87]

Clinically, decreased fertility is a well-recognized consequence of cryptorchidism. Data derived from orchiopexies performed in the 1950s to 1970s indicate that paternity is impaired in approximately 10% to 13% of boys born with one undescended testis and in 33% to 35% of those born with two undescended testes.[88,89] These rates are not significantly different from the control infertility rate of 7% in unilateral cryptorchids but are significantly lower than control in bilateral cryptorchids.[89] Although histologic deterioration was thought to be worse with higher-positioned testes, paternity (which does not necessarily correlate with histology of the undescended testis in cases of unilateral maldescent) may be similar in both abdominal and extra-abdominal unilateral undescended testes.[90] The serum level of inhibin B, an indicator of Sertoli cell function and seminiferous tubule integrity, is lower in boys with a history of cryptorchidism. This may predict impaired spermatogenesis later in life, although there is much overlap of hormone levels between fertile and infertile men.[89] Therefore, it is still not clear whether early orchiopexy ultimately improves fertility, but serum inhibin B levels are suggestive of this trend.[91] Without treatment, bilateral cryptorchidism ultimately results in infertility. Antisperm antibodies, abnormalities of the epididymis and vas deferens, and surgical injury to the vas deferens during orchiopexy may also contribute to infertility in patients with a history of cryptorchidism.

Malignancy

Given that in all men the lifetime risk of testicular cancer is 0.3% to 0.7%,[92] there is a 3.7- to 7.5-fold increased risk in individuals born with an undescended testis.[93] Approximately

10% of all testis tumors develop in men with a history of an undescended testis. Whereas previous data suggested a four-fold greater incidence of malignant degeneration in an abdominal compared with an inguinal testis, more recent studies failed to confirm this increased risk. The observation that 10% to 20% of testicular tumors in cryptorchid patients occur in the normally descended testis[94,95] suggests that an intrinsic abnormality is present in both testes even if only one is undescended. It was hoped that earlier orchiopexy (age <2 years) would prevent testis cancer, but the data on the timing of orchiopexy are conflicting in this regard.[96,97]

Despite the increased risk compared with the general population, the likelihood of developing testicular cancer in a man with a history of cryptorchidism is no more than 1 in 2000. For this reason, removal of undescended testes is not warranted in the general case. Orchiopexy allows easy examination of the scrotal testis for earlier detection in cases of testicular cancer. The most common testicular tumor in untreated undescended testes is seminoma, whereas the most common type in successfully treated testes is embryonal carcinoma.[94]

Testicular biopsy at the time of orchiopexy may reveal carcinoma in situ (CIS) in both the undescended and the contralateral descended testis.[98] CIS is more common in abdominal testes than in more caudal cryptorchid testes,[99] but such premalignant changes may not be seen in cryptorchid testes treated before adulthood.[100] Although some cases of CIS progress to testicular tumors, the fact that most do not makes the clinical significance and management of this finding controversial. Therefore, the routine use of testicular biopsy at the time of orchiopexy is not generally recommended. However, biopsy is recommended for patients with prune-belly syndrome, abnormal karyotype, ambiguous genitalia, or age greater than 12 years.[97]

Inguinal Hernia

About 90% of undescended testes are associated with an occult inguinal hernia, especially those with minimal descent and those coupled with epididymal abnormalities. Ectopic testes are associated with an inguinal hernia in about 50% of cases. Conversely, up to 6% of inguinal hernias are associated with an undescended testis.[101] Repair of the hernia, if present, is an integral part of orchiopexy.

Risk of Torsion

Testicular torsion occurs more frequently than normal in undescended abdominal testes and is associated with poor surgical salvage rates (~10%).[102] Torsion of the testis in the inguinal canal is unusual. If an undescended testis undergoes postnatal torsion, it can indicate the presence of testicular tumor.[103] Torsion in an undescended testis should be suspected in any male with groin or abdominal pain, an empty hemiscrotum, and a negative surgical history.

Risk of Trauma

An inguinal testis is subject to blunt traumatic injury by compression against the pubic bone. This risk is prevented by orchiopexy or orchiectomy.

Psychological Factors

Preoccupation with a solitary scrotal testis, uncertainty regarding the presence and location of a cryptorchid testis, embarrassment with peers and sexual partners, a tarnished body image, fear of sterility, and other adverse concerns and personality changes may result as a consequence of cryptorchidism.[104] Theoretically, orchiopexy or placement of a testicular prosthesis could prevent such psychological fears, although this has not been formally studied.

NONSURGICAL THERAPY

Medical treatment for cryptorchidism is based on the hormonal dependence of testicular descent.[105] Both hCG and gonadotropin-releasing hormone (GnRH) or luteinizing hormone–releasing hormone (LHRH) have been used to induce testicular descent. Systemic testosterone has not been used, because the key factor in testicular descent is a high *local* level of androgens (a paracrine effect).

Agents

Human Chorionic Gonadotropin

hCG is structurally similar to LH and stimulates endogenous testosterone production by the testis. An example of a therapeutic dose is 1500 units given intramuscularly per square meter of body surface area twice a week for 4 weeks. The total dose should not exceed 15,000 units. In the United States, hCG is the only approved medication for use in cases of undescended testis. A testicular descent rate of 25% is achieved with hCG, and 18% with GnRH.

Luteinizing Hormone–Releasing Hormone

Therapy with LHRH is not approved for use in the United States. A typical course of therapy consists of 1.2 mg/day, in divided doses, for 4 weeks. Trials comparing intranasal LHRH with placebo yielded complete testicular descent rates of approximately 20% versus 5%, respectively.[106] Neoadjuvant GnRH treatment before orchidopexy was found to improve the fertility index in prepubertal cryptorchidism.[107]

Buserelin

Buserelin, a synthetic LHRH superanalogue, is administered in very small doses, such as 10 μg every other day for 6 months. It induces testicular descent in 17% of cryptorchid boys,[108] which is similar to the results achieved with either LHRH or hCG. Buserelin may also improve germ cell histology and spermiograms obtained after spontaneous descent or orchiopexy.[109] It is available in Europe but it is not approved for use in the United States. Another GnRH analogue, naferelin, has demonstrated preliminary results similar to those of buserelin.[110]

Success of medical therapy is better for lower testes,[111] although inclusion of retractile testes in some studies may overestimate the success of medical therapy. After successful therapy, the patient should be reexamined periodically, because approximately 15% of successfully treated testes reascend. If a course of medical therapy is unsuccessful, an additional course with the same or another agent is not likely to be beneficial.

Hormone administration is contraindicated in newborns, in patients who are unlikely to respond (e.g., those with postoperative undescended testes or ectopic testes), in patients who cannot anatomically respond (e.g., boys with prune-belly syndrome), and in patients beyond puberty who are endocrinologically normal.

Penile enlargement, frequent erections, scrotal rogation and pigmentation, increased appetite and weight gain, and aggressive behavior are all seen to some degree with hormonal administration. A potential serious complication of excessive hormonal therapy is premature closure of the epiphyseal plate, limiting long bone growth. Possible imprinting due to high androgen levels in the central nervous system has not been proven to occur but remains a remote possibility.

The overall efficacy of medical treatment in cryptorchid boys is less than 20% and significantly depends on the pretreatment testicular location. Surgery remains the gold standard.

SURGICAL THERAPY

Surgical Anatomy

The testis is supplied by the spermatic cord, which contains the ilioinguinal (L1) and genital branches of the genitofemoral nerve (L1-L2), the cremaster muscle, the testicular vessels, the vas deferens, sympathetic and parasympathetic nerves, and the remnants of the processus vaginalis. The fascial layers of the spermatic cord and scrotum include the external spermatic fascia (an extension of the external oblique fascia), the cremasteric or middle spermatic fascia (an extension of the internal oblique fascia), and the internal spermatic fascia (an extension of the transversalis fascia).

The testicular artery, also termed the gonadal or internal spermatic artery, is a branch of the abdominal aorta. The testis also receives blood supply via the cremasteric (external spermatic) artery and the artery of the vas deferens, which are branches of the inferior epigastric and inferior vesical arteries, respectively. Venous drainage of the testis is via the pampiniform plexus of veins, which drains through the gonadal vein into the renal vein on the left and the inferior vena cava on the right. The gonadal vessels course in the retroperitoneum ventral to the ureter before entering the internal inguinal ring just lateral to the inferior epigastric vessels. In 1960, Prentiss and colleagues described the indirect course of the testicular vessels in the retroperitoneum and methods to achieve length by releasing the lateral attachments, thus creating a straight course to the inguinal canal.[112] Lymphatic drainage of the testis is to the retroperitoneal lymph nodes adjacent to the aorta and vena cava but may be altered after orchiopexy to include the superficial inguinal lymph nodes.

Surgery for the Palpable Testis

The historical outcomes of surgical therapy for cryptorchidism are contrasted in Table 43-2.

Table 43-2 **Historical Results of Surgical Therapy for Cryptorchidism**

Type of Surgery	Success Rate (%)
Surgery based on testicular position	
Abdominal	74
Peeping (internal inguinal ring)	82
Inguinal	87
Prepubic	92
Surgery based on surgical procedure	
Inguinal orchiopexy	89
Transabdominal orchiopexy	81
One-stage Fowler-Stephens orchiopexy	67
Two-stage Fowler-Stephens orchiopexy	77
Microvascular autotransplantation orchiopexy	84

Data from Docimo SG. The results of surgical therapy for cryptorchidism: a literature review and analysis. *J Urol.* 1995,154:1148-1152.

Inguinal Orchiopexy

Examination under anesthesia is performed before any orchiopexy to confirm the choice of incision site. For an inguinal orchiopexy, an inguinal incision is made in the lower abdominal skin crease. After Scarpa's fascia is opened, dissection should be done carefully in case the testis is in the superficial inguinal pouch between the external oblique and Scarpa's fascia. The inguinal ligament and external ring are exposed, and the external oblique is opened in the direction of its fibers. The ilioinguinal nerve is carefully preserved. Cremasteric muscle fibers are separated sharply to expose the spermatic cord. As the testis is drawn out of the wound, the gubernaculum is carefully thinned and divided, with care taken to prevent injuring a looping vas deferens that may precede the testis into the canal. The anterior wall of the tunica vaginalis is opened to expose the testis. Typically, any testicular or epididymal appendages are excised. The spermatic cord is freed proximally to the internal inguinal ring, and all tethering cremaster muscle fibers are teased off the cord or divided. The hernia sac is separated from the anteromedial aspect of the spermatic cord at the level of the internal inguinal ring. The hernia sac is ligated at the internal inguinal ring with absorbable suture, and the ligature is held to help expose the retroperitoneal space if additional dissection is necessary to gain cord length. If the cord is still short, preventing a tension-free orchiopexy, the internal inguinal ring is opened laterally, and the peritoneum is bluntly elevated off of the testicular vessels. The lateral spermatic fascia is sharply divided, allowing the vessels a straighter course to the scrotum.[112] The Prentiss maneuver, which consists of dividing the inferior epigastric vessels and transposing the testicular vessels medially to provide a straight vascular course to the scrotum, may be performed, although the length achieved by this maneuver is probably insignificant.

Although there has been some theoretical concern, testicular fixation or intrinsic developmental alterations of the cryptorchid testis do not elicit an autoimmune response against sperm surface antigens at puberty.[113] Fixation in the scrotum has been achieved in various ways. Commonly, a subdartos pouch is created in the anterior wall of the scrotum. The testis may be secured by tightening the dartos behind it or by passing a stay suture through the inferior wall of the scrotum. The placement of this suture is beneath the lower pole of the testis, in gubernacular tissue, in order to avoid the risk of testicular atrophy.[114] The vascular pedicle is inspected to confirm the absence of tension and torsion. The procedure is generally performed on an outpatient basis unless comorbidity requires overnight observation.

If a scrotal stay suture is used, it is usually removed 1 week after surgery. Patients are seen 6 months postoperatively to determine testicular position and size. Recommendations are made for evaluation at puberty to confirm testicular growth and to teach self-examination. For those with congenital or surgical monorchia, warnings are given regarding the benefits of scrotal protection during contact sports activities.

At the time of orchiopexy, ectopic tissue may rarely be identified adjacent to the testis. Examples include spleen and liver tissue (from splenogonadal or hepatogonadal fusion) and adrenal tissue in the form of an adrenal rest. Preoperative awareness and intraoperative recognition of these variations in anatomy should allow proper management and prevent complications.

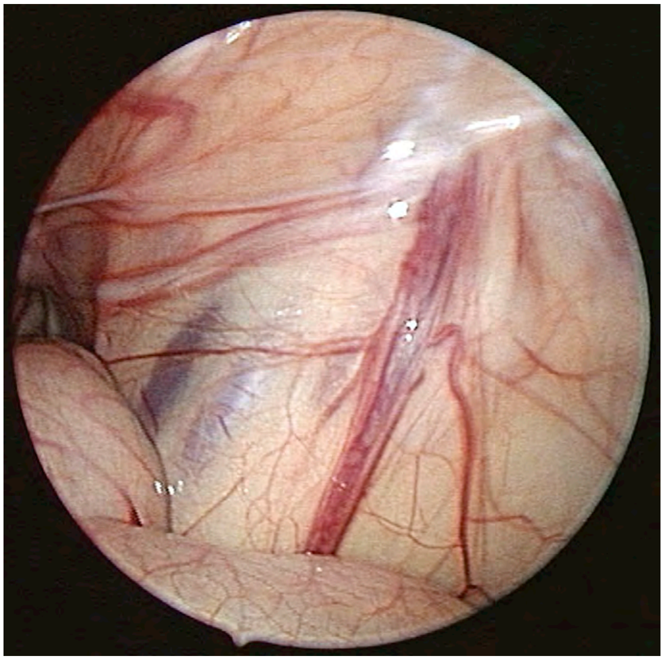

Figure 43-5 Laparoscopic view of normal right internal ring anatomy, including vas and testicular vessels exiting a closed internal ring.

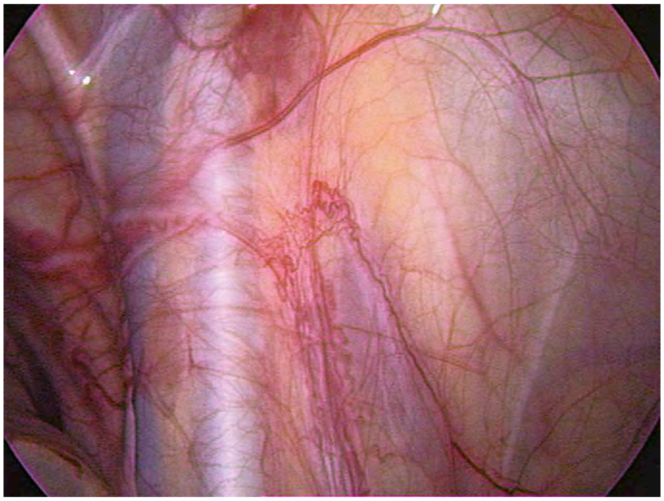

Figure 43-6 Laparoscopic view of abnormal right internal ring anatomy, including vas and blind-ending testicular vessels adjacent to a closed internal ring. (From Baker LA, Jordan GH. Laparoscopic management of the nonpalpable testicle. In: Graham SD Jr, ed. *Glenn's Urologic Surgery*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2004:1015-1026. Used by permission from Lippincott Williams & Wilkins.)

Transscrotal Orchiopexy

Testes that are low in the canal and are believed to be ectopic are good candidates for a transscrotal approach.[115,116] In this approach, the inevitable scrotal incision is made at the beginning of the procedure. The testis is manipulated through the incision, and a stay suture is placed. The ectopic gubernacular attachments are divided, looking for the course of the vas deferens. Any testicular or epididymal appendages are excised. The processus vaginalis is probed to check for patency. In 20% of cases, an inguinal incision will be needed to correct the hernia.[116] The testis and cord are mobilized through the scrotal incision until enough laxity is obtained to achieve orchiopexy without tension. Fixation is achieved as described previously. The technique has been especially useful for reoperative orchiopexy after prior inguinal hernia repair when the testis is close to the scrotum.

Surgery for the Nonpalpable Testis

Surgery for the nonpalpable testis must determine whether a testicle is present and, if one is found, either place it in the scrotum or remove it. The easiest and most accurate way to locate an intra-abdominal testis is by diagnostic laparoscopy,[117] which can be followed by laparoscopic orchiopexy methods to simultaneously achieve therapeutic goals if a testis is found.[118] Contraindications to laparoscopy include prior abdominal surgery with potential peritoneal adhesions or a body habitus that will not allow for proper placement of abdominal wall ports and laparoscopic instruments.

Laparoscopic Surgery

DIAGNOSTIC LAPAROSCOPY

As in adults, pediatric diagnostic laparoscopy requires placement of a nasogastric tube and a Foley catheter. Peritoneal access for carbon dioxide insufflation is achieved with the use of techniques specific to the infant and young child.[119] With the patient in Trendelenburg position, each internal ring of the inguinal canal, located just lateral to the inferior epigastric vessels, is inspected. At each internal ring, the spermatic vessels approach in a cranial to caudal direction while the vas deferens courses medial to lateral. Possible anatomic findings on the side of the nonpalpable testis include the following[82]:

1. The spermatic vessels enter the inguinal canal (40%) (Fig. 43-5).
2. A canalicular or peeping testis is found (11.2%) (see Fig. 43-2).
3. The spermatic vessels end blindly (9.8%) (Fig. 43-6).
4. A viable intra-abdominal testis is identified (37%) (Fig. 43-7).

If the vas and spermatic vessels exit the internal inguinal ring, groin pressure can be applied to express a canalicular testis back into the abdomen. If not, inguinal and scrotal exploration for a testicle or testicular remnant should be performed even if the internal inguinal ring is closed, although this is a controversial point.[120] If vessels proceed through the internal ring and there is a closed internal ring, the likelihood of functioning testicular tissue is between 3% and 25%, whereas if a patent internal ring is present, the groin should be explored, because the testis could be present in 75% to 97% of cases.[121]

The observation of blind-ending spermatic vessels is the sine qua non of a vanishing testis, which is considered to be caused by prenatal testicular torsion. In such cases, no further exploration is warranted. If a vas deferens and epididymis are seen but blind-ending spermatic vessels are not identified, testicular-epididymal disjunction may be present, and further exploration[122] near the pericolic gutter or the lower pole of the kidney[123] is required. Placement of secondary cannulas may assist in this examination by allowing retraction and reflection of the colon. If no testis or testicular vessels are found, the imperative to continue exploration and examine the renal hilum remains controversial. As with preoperative

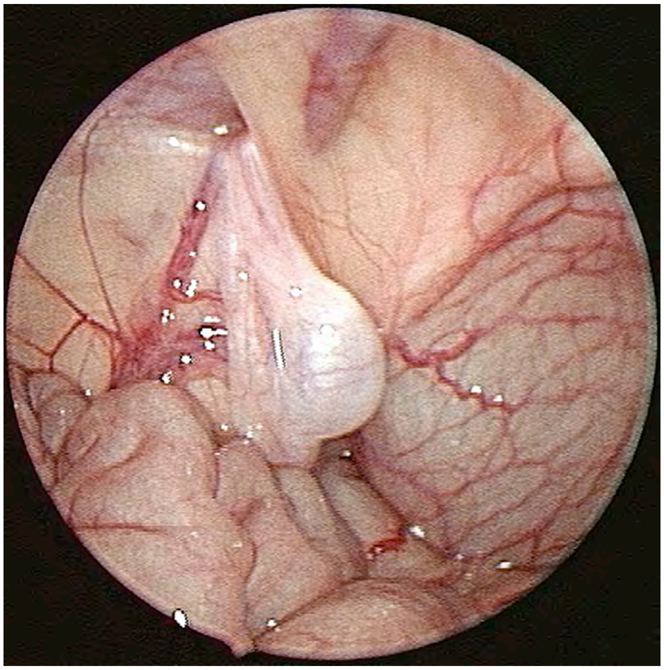

Figure 43-7 Laparoscopic view of abnormal left internal ring anatomy, including an intra-abdominal testis obscuring the view of its vas and testicular vessels adjacent to the open left internal ring. (From Baker LA, Jordan GH. Laparoscopic management of the nonpalpable testicle. In: Graham SD Jr, ed. *Glenn's Urologic Surgery.* 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2004:1015-1026.)

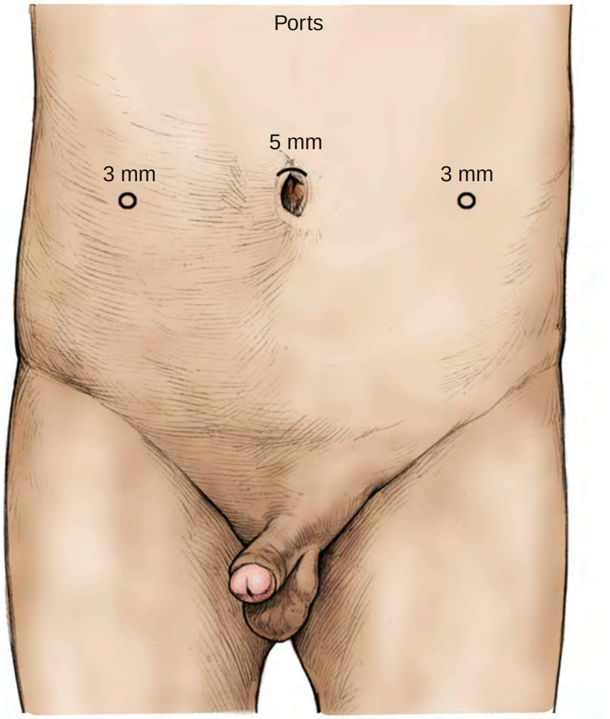

Figure 43-8 Laparoscopic port placement for standard orchiopexy. A radially dilating trocar is used for open access in the umbilicus, and 2-, 3-, or 5-mm instruments are used laterally as shown. (From Mathews R, Docimo S. Laparoscopy for the management of the undescended testis. *Atlas of the Urologic Clinics of North America.* 2000;8:91-102. With permission from Elsevier.)

localization, radiographic imaging to look for a testis postoperatively has limited value.

When an intra-abdominal testis is found, the appearance of the testis and its position in relation to the internal inguinal ring are noted. Testes lying more than 1 to 2 cm above the ring may not reach the scrotum without division of the testicular vessels.[82] Abnormal testes and those that are clearly dissociated from the vas deferens and epididymis may be removed as the primary form of therapy, depending on the clinical situation and the wishes of the family.

Preoperative administration of hCG has been used by some to try to stimulate descent of the testis to a palpable position and thereby obviate the need for laparoscopy.[124,125] However, approximately 50% of these patients can receive no potential benefit from hormonal therapy because they have an absent or atrophic testis. Virtually all patients with nonpalpable testes will require surgical intervention, even if there is a response to hCG, so the value of hormonal therapy in this situation is debatable.

Therapeutic Laparoscopy

There are three laparoscopic procedures that are commonly performed to treat the intra-abdominal testis:

1. Primary one-stage orchiopexy with preservation of the spermatic vessels
2. Orchiectomy
3. Division of the spermatic vessels as the first stage of a two-stage Fowler-Stephens orchiopexy[126]

The second stage of a two-stage Fowler-Stephens orchiopexy can also be performed laparoscopically. In addition to these procedures, laparoscopic-assisted microvascular autotransplantation has been described.[127]

Laparoscopic orchiopexy has developed as a standard technique for treatment of the intra-abdominal testis because of its distinct advantages, which include

1. The ability to achieve an extensive vascular dissection to the origin of the gonadal vessels
2. Dissection of the proximal vessels without disturbance to the peritoneum between the vas deferens and the distal spermatic cord, thus preserving the option of a Fowler-Stephens approach
3. High-magnification (15×) and improved visualization during mobilization of the proximal spermatic vessels and gubernaculum
4. The ability to create a new internal ring medial to the inferior epigastric vessels, to achieve a straight vascular course to the scrotum
5. Minimal morbidity in older children and adolescents

To perform laparoscopic orchiopexy after diagnostic laparoscopy,[128] two 2- to 5-mm trocars are placed under direct vision from the umbilical camera (Fig. 43-8). These trocars are placed in the anterior axillary line, just below the level of the umbilicus, on each side. The peritoneum is incised distal to the vas and processus vaginalis and lateral to the spermatic vessels (Fig. 43-9). The peritoneal triangle overlying the distal spermatic cord is left intact to enhance collateral circulation to the testis and to allow a Fowler-Stephens approach, if necessary.[129] A plane of dissection is developed behind the cord (or gubernaculum), and retraction allows identification of the distal extent of the vas deferens. The gubernaculum is divided distal to the vas by electrocautery, and the testis is retracted medially to allow extensive dissection of the vessels for length. If additional length is needed, the proximal peritoneum can be

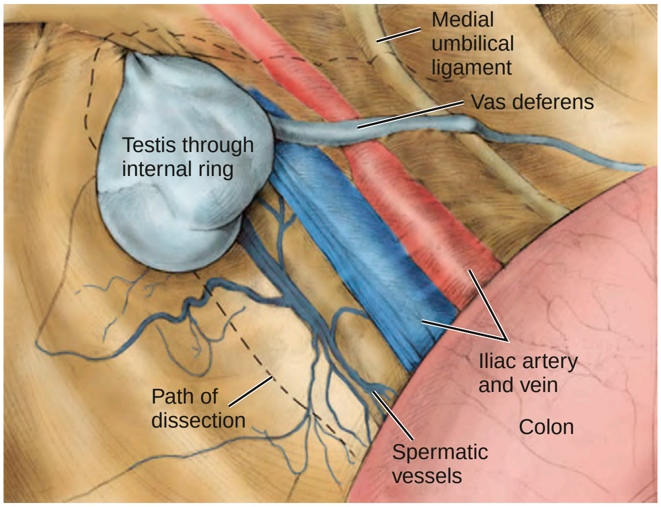

Figure 43-9 The laparoscopic anatomy of the undescended left testis. The dotted line indicates the initial peritoneal incision. (From Mathews R, Docimo S. Laparoscopy for the management of the undescended testis. *Atlas of the Urologic Clinics of North America.* 2000;8:91-102. With permission from Elsevier.)

carefully stripped off the anterior surface of the spermatic vessels, leaving the distal peritoneum intact. The testis is drawn toward the opposite inguinal canal as a rough indicator of adequate vascular length. Most testes can be brought down with the spermatic vessels intact. A 2-mm grasper is passed from the ipsilateral trocar, over the pubis, and through an anterior scrotal incision. A radially dilating trocar sleeve is introduced over this grasper into the abdominal cavity and is dilated to 10 mm (Fig. 43-10).[128] A laparoscopic Allis clamp is used to draw the testis out through the scrotal incision as the scrotal trocar is removed. The testis is fixed in a subdartos pouch as for an inguinal orchiopexy. The intra-abdominal gas is expressed, and the trocar sites are closed. The patient is allowed to go home on the day of surgery. Postoperative care is identical to that for an open orchiopexy.

If indicated, laparoscopic orchiectomy is similar to laparoscopic orchiopexy except that, after mobilization of the testis, the vascular pedicle and vas deferens are ligated with endoscopic hemoclips and divided. One 5-mm trocar site is necessary for the clip applicator. The testis is then passed out an abdominal port with graspers, and the procedure is completed as described previously.

Primary division of the testicular vessels as part of a two-stage Fowler-Stephens orchiopexy is a reasonable option if primary orchiopexy is judged to be unwise because of short testicular vessels.[126] The procedure is easily performed laparoscopically, with identification and hemoclip ligation of the testicular vessels. At a second-stage procedure, usually at least 6 months later, the orchiopexy is completed laparoscopically, with special attention to preservation of the collateral blood supply to the testis.[128]

A small testicular remnant, sometimes referred to as a “nubbin,” may be identified during exploration for the nonpalpable testis and represents the remains of a vanishing testis. Approximately 10% contain tubular structures with germ cell elements that could potentially undergo malignant degeneration.[48] Some practitioners remove these nubbins based on the presence of germ cells, not the incidence of testicular cancer, which remains undefined for this entity.

Surgical outcomes for the intra-abdominal testis using open versus laparoscopic methods are contrasted in Table 43-3.

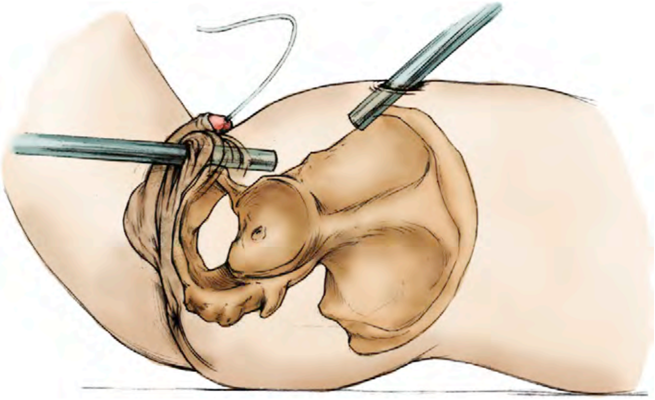

Figure 43-10 Schematic drawing demonstrates the course of the scrotal trocar over the pubic bone and into the peritoneal cavity. (From Mathews R, Docimo S. Laparoscopy for the management of the undescended testis. *Atlas of the Urologic Clinics of North America.* 2000;8:91-102. With permission from Elsevier.)

Despite common belief, on a population basis, initial laparoscopic evaluation of the clinically nonpalpable testicle has been shown to have a cost-saving advantage over initial inguinal-scrotal exploration when reusable laparoscopic equipment is primarily used, disposable equipment costs are kept low, and operating room time for diagnostic laparoscopy meets national standards.[130]

Open Surgery

Diagnostic laparoscopy for the intra-abdominal testis can be followed by open surgical orchiopexy. An option is the Jones approach, an extraperitoneal approach that utilizes a higher incision than the standard inguinal orchiopexy, extending from the anterior superior iliac spine medially.[131,132] The retroperitoneum is explored through a muscle-splitting incision, and orchiopexy is performed in the usual fashion if a testis is found.

Fowler-Stephens orchiopexy[129] is useful for the short testicular vessels. The testicular vessels are divided, and the testicular blood supply relies on collateral circulation of the artery of the vas deferens and the cremasteric artery. This method can be performed as an open procedure or laparoscopically in one or two stages. However, an open one-stage Fowler-Stephens procedure must be planned in advance before the cord is skeletonized. Temporary occlusion of the gonadal vessels, incision of the tunica albuginea, and inspection of the testis for color and arterial bleeding can be used to confirm adequate collateral blood supply (the Fowler-Stephens test), although this does not necessarily correlate with lack of testicular atrophy.[133] Traditionally, division of the testicular artery has been performed near its origin, but an alternative recently proposed by Koff and Sethi is to divide the testicular artery close to the testis, to preserve collateral blood flow to the vasal artery from the proximal spermatic vessel.[134] The Fowler-Stephens approach requires a vas deferens with adequate length to extend the testis into the scrotum. Contraindications include segmental vas atresia or a detached epididymis, which may interrupt the collateral blood supply to the testis. The Fowler-Stephens technique must be performed meticulously. Testicular atrophy may occur in 20% to 50% of the cases.[134] Although the use of hCG before Fowler-Stephens orchiopexy has been suggested to improve collateral blood flow,[125] there is no experimental or clinical evidence to support this approach.[135]

Table 43-3 **Success Rates[*] of Open versus Laparoscopic Orchiopexy from Two Large Published Series**

	Primary Orchiopexy		One-Stage F-S		Two-Stage F-S	
	n	%	*n*	%	*n*	%
Open[133]	80	81.3	321	66.7	56	76.8
Laparoscopic[141]	178	97.2	27	74.1	58	87.9

[*] Success was defined as scrotal position and lack of atrophy.

F-S, Fowler-Stephens orchiopexy; *n*, number of testes.

From Baker LA, Lorenzo A, Jordan GH, Docimo SG. *Laparoscopy and Cryptorchidism. Minimally Invasive Approaches to Pediatric Urology.* London: Taylor & Francis; 2005:161-176. Used by permission from Taylor & Francis.

If the spermatic cord has been dissected and cord length is insufficient for scrotal placement, the options are orchiectomy or staged orchiopexy. The staged orchiopexy is usually performed unplanned.[136] In the first stage, the testis is fixed without tension to the lowest possible site, usually the periosteum over the pubis. The testis and spermatic cord can be wrapped with a Silastic membrane, to facilitate dissection during the second-stage procedure, although there may be little benefit to this maneuver. The second-stage procedure is performed 6 to 12 months later to complete the orchiopexy.

If there is only one testis with extremely short vessels, a microvascular autotransplantation can be considered. Autotransplantation is a technically challenging procedure, and atrophy rates may approach 20%,[137] although higher success rates have been reported.[138] Therefore, this approach may be considered excessive if there is a contralateral normal scrotal testis. Laparoscopy may help identify those testes that would require such an approach.[127] Microvascular autotransplantation requires plastic surgical anastomosis of the testicular vessels to the ipsilateral inferior epigastric artery and vein. The scrotal pouch is developed. After the inferior epigastric pedicle is prepared, the testis is dissected as for a Fowler-Stephens approach, but the vessels are divided as high as possible. A microvascular anastomosis is then performed by someone familiar with the technique. Postoperatively, bed rest is maintained for 48 hours; the use of anticoagulants has not been routinely described.

Surgery after prior failed orchiopexy or for testicular ascent after hernia repair can be especially challenging.[139] Parents must be aware that the procedure might result in orchiectomy if sufficient vascular length cannot be achieved. The approach depends on the position of the testis but usually proceeds through a standard inguinal incision. Sometimes, an en bloc dissection of the cord with surrounding structures is necessary to preserve the vessels, but in other circumstances, the vascular pedicle and vas can be dissected free of surrounding structures in a fairly straightforward manner. The method of dissection depends on the anatomy at hand, but the principles of orchiopexy are similar to those in the primary situation.[140] It is important to realize that the testis often has flipped up over a fixed cord, so the orientation of the testicle is unpredictable.

COMPLICATIONS OF ORCHIOPEXY

Complications of orchiopexy are relatively uncommon. The most important surgical complication of orchiopexy is *testicular atrophy*, which may result from four causes:

1. Injury to the spermatic vessels during standard orchiopexy
2. Tension on the spermatic vessels with subsequent ischemia
3. Inadvertent torsion of the spermatic vessels when passing the testis into the scrotum
4. Intentional ligation of the vessels as part of a Fowler-Stephens orchiopexy

Any of the complications of inguinal hernia repair can also occur during orchiopexy. Testicular retraction may result from short testicular vessels, inadequate mobilization of the testicular vascular pedicle, incomplete division of the cremasteric muscle fibers to the testis, or improper scrotal fixation of the testis.

CONCLUSION

The etiology of testicular maldescent remains unknown, although recent advances in molecular understanding of testicular descent are shedding some light. Whatever the underlying cause, the undescended testis deserves treatment early in life to prevent loss of spermatogenic potential and to allow early detection of testicular malignancy, should it occur. Treatment can be through hormonal manipulation or surgery, and the choice depends on age and testicular location. Surgery for the palpable testis remains most commonly an inguinal approach with retroperitoneal dissection as necessary. The nonpalpable testis is most commonly approached laparoscopically, and the success rate of laparoscopic orchiopexy may exceed that of more traditional open approaches. In the future, a more complete understanding of the biology of testicular descent may allow more specific nonsurgical therapy or decrease the need for orchiopexy.

REFERENCES

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CHAPTER 44

PATENT PROCESSUS VAGINALIS

Prasad P. Godbole and Mark D. Stringer

A processus vaginalis (PV) develops as a result of descent of the testis. If patent, it may be asymptomatic, or it may manifest with a congenital inguinal hernia or hydrocele. The difference between a congenital inguinal hernia and a hydrocele relates to the caliber and content of the processus. With a hernia, the processus is wide and contains intra-abdominal viscera, whereas in a congenital hydrocele, the processus is narrow and contains only peritoneal fluid. This chapter focuses on the patent PV rather than inguinal hernia.

EMBRYOLOGY

The development of the PV is related to the descent of the testis.[1] A PV is identified in all species where there is migration of a male gonad through the inguinal canal.[2] Testicular descent is understood to occur in two sequential phases, the transabdominal and the inguinoscrotal phase, each under different hormonal controls.[3] A key structure in the transabdominal phase is the gubernaculum, which is seen as a short, thin column of mesenchyme connecting the ambisexual gonad and the urogenital ridge to the inguinal region. In the male fetus, the caudal end of the gubernaculum enlarges (the swelling reaction) by mitosis and deposition of hyaluronic acid.[4,5] This swelling reaction holds the testis closely to the future internal inguinal ring. The gubernacular swelling reaction is under the hormonal control of insulin-like peptide 3 (INSL3), which is produced by fetal testicular Leydig cells, augmented by anti-müllerian hormone (AMH, also called müllerian inhibiting substance, or MIS), and androgen.[6,7]

The PV results from an outpouching of mesothelial cells from the coelomic cavity into the substance of the gubernacular mesenchyme. The proximal part of the PV is first visible at about the 8th week of intrauterine life.[8] The gubernaculum is divided by the invading PV into three parts: the *plica gubernaculi*, the column of mesenchyme that extends from the caudal pole of the testis to the distal extremity of the PV; the *pars vaginalis*, a thin layer of mesenchyme surrounding the PV, from which the cremaster muscle develops; and the *pars infravaginalis*, the gubernacular mesenchyme distal to the processus, into which it continues to grow (Fig. 44-1).[9]

Heyns showed that the bulb of the gubernaculum is the same size as the testis and its caudal end lies loose under Scarpa fascia during the inguinoscrotal phase of descent.[10] The distance to the scrotum is several times longer than the size of the gubernaculum itself, indicating that active migration of the gubernaculum to the scrotum is necessary for inguinoscrotal descent of the testis.[11,12] Histologic examination of the neonatal rat gubernaculum revealed that cell division occurred most rapidly at the tip of the gubernacular bulb and its contained PV, consistent with active elongation.[13,14] This has been shown to be at least partly influenced by calcitonin gene-related peptide (CGRP), which is released by the sensory neural component of the genitofemoral nerve.[15-17] Androgen blockade abolishes the increased rate of cell proliferation within the gubernacular tip, indicating that androgens are necessary to permit the proliferative response of the gubernaculum to CGRP.[18]

The PV acts as a conduit for the intra-abdominal fetal testis to pass to the scrotum, and it too is likely to be influenced by the genitofemoral nerve and CGRP.[19] CGRP has been shown to cause fusion of hernial sacs and obliteration of the peritoneal surface in vitro within 48 hours, thereby supporting the concept that the genitofemoral nerve and CGRP control not only testicular migration but also obliteration of the PV after testicular descent (see later discussion).[1]

After migration of the testis into the inguinal canal, the PV descends further with the testis. The patent PV transmits the fetal intra-abdominal pressure to the testis during its inguinal migration, and this hydraulic force may assist the process of testicular descent.[10] In girls, the PV reaches only a rudimentary stage of development, identifiable as the canal of Nuck.

HISTOLOGY

Histopathologic examination of the PV demonstrates an inner surface of mesothelium supported by loose connective tissue containing blood vessels and peripheral nerves.[8,20] An inguinal hernia sac has an additional layer of irregularly arranged smooth muscle, which is also present in a patchy distribution in the patent PV associated with a hydrocele but is absent in the obliterated PV. The significance of this smooth muscle is uncertain, but failed apoptosis of this muscle may have a role in the persistence of a PV.[21]

The tiny, bright yellow nodule seen on the outer surface of some processus sacs in boys at the time of surgery is a benign adrenal rest.[22,23] In one study, ectopic adrenocortical tissue was found in 4% of boys at ligation of a patent PV for communicating hydrocele.[24]

NATURAL HISTORY OF THE PROCESSUS VAGINALIS

There is little agreement regarding the timing or process of closure of the PV.[25] Two methods of investigation have yielded information: assessment of the patency of the contralateral processus in children with a unilateral inguinal hernia, and autopsy studies examining patency of the processus at various ages. The former method of study may be misleading, because children with an inguinal hernia by definition have an intrinsic abnormality of their PV.

In a review of the literature in 1962, Sparkman concluded that a patent PV was present in 57% of contralateral groin explorations in children with a unilateral inguinal hernia.[26] Rowe and colleagues demonstrated a contralateral PV patency rate of 63% in the first 2 months of life among children undergoing surgery for an inguinal hernia.[27] After 2 months, there was a steady decline in the incidence of patency until the age of 2 years, when it leveled off. From the age of 2 to 16 years, the patency rate was 40%. Right-sided patency was more common than left. The authors concluded that the PV continues to undergo obliteration after birth until about 2 years of age.

By injecting a fine barium emulsion into the peritoneal cavity of 40 stillborn infants, Mitchell was able to demonstrate

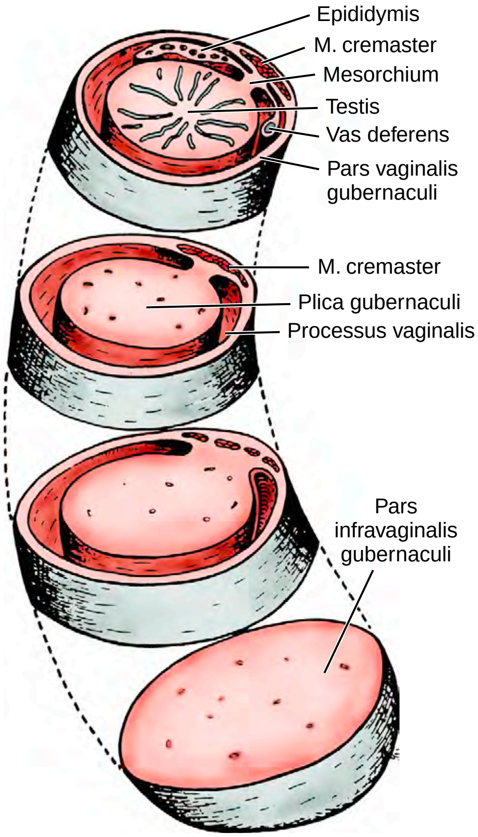

Figure 44-1 Schematic sectional representation of the processus vaginalis and gubernaculum testis, near the completion of testicular descent. M., muscularis. (From Clarnette TD, Hutson JM. The genitofemoral nerve may link testicular inguinoscrotal descent with congenital inguinal hernia. *Aust N Z J Surg.* 1996;66: 612-616. Reproduced with permission.)

that closure of the PV occurs before birth in a proportion of cases.[28] The processus was completely closed on both sides in 6 (21%) of 29 term stillbirths but in only 1 (9%) of 11 immature fetuses. Other autopsy studies have indicated that the PV is patent in about 80% of newborns, decreasing to about 60% by the end of their first year.[29] The patency rate has varied between 15% and 30% in similar studies in adults.[29,30] Therefore, in a significant proportion of men, the PV never obliterates but an overt hydrocele or hernia does not develop.

Boys with cryptorchidism frequently have a patent PV.[31-33] In one study of 102 males with cryptorchidism aged 1 to 33 years (mean, 10 years), a patent PV was found in 58%.[34] Patency rates were not clearly correlated with the age of the patient. Other authors have found even higher rates of PV patency in boys with undescended testes.[33]

The exact mechanism of obliteration of the PV has not yet been well defined. Momoh examined the anatomy of the hernial sac in 100 children with an inguinal hernia in an attempt to elucidate the mechanism of obliteration of the PV.[35] Three mechanisms were postulated: (1) progressive fibrous obliteration of the processus in a cephalad direction beginning above the epididymis; (2) compression of the processus into a tubular structure followed by fibrous obliteration; and (3) segmentation of the processus followed by fibrous obliteration. The first mechanism was considered to be the most common. In all cases, the distal processus persists as the tunica vaginalis.

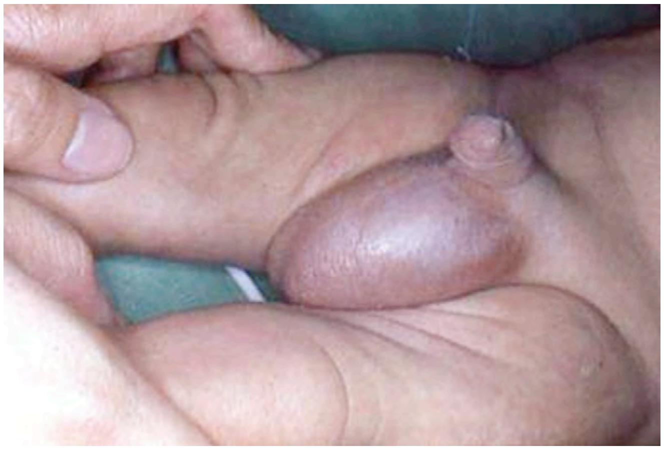

Figure 44-2 Left-sided hydrocele. Note the slight bluish discoloration of the scrotum and absence of an ipsilateral groin swelling.

At a molecular level, CGRP may be a key component in closure of the PV. In an organ culture system of human infant hernial sacs, Hutson and colleagues showed that CGRP can induce PV fusion and that CGRP receptors are present on PV mesenchymal fibroblasts but not on PV epithelial cells.[36] CGRP present in the genitofemoral nerve may therefore trigger the release of another factor that results in subsequent fusion of the PV. One hypothesis is that hepatocyte growth factor (HGF) may act as an intermediary in this way, because receptors for this growth factor can be found in the PV and HGF can also cause PV fusion in vitro.[37] Understanding the molecular mechanisms of PV obliteration could lead to the development of nonsurgical treatment of patent PV through local administration of agents that promote fusion.

There is additional evidence that androgenic stimulation may indirectly be required for PV closure. In a prospective analysis of PV patency, epididymal anomalies, and cryptorchidism in boys undergoing inguinal surgery, Barthold and Redman found that closed, partially closed, and open PVs were associated with an abnormal epididymis in 14%, 36%, and 69% of the cases, respectively.[38] Epididymal anomalies were associated with patency of the PV regardless of testicular position. The authors concluded that, because androgenic stimulation may be required for epididymal development, it may also be necessary for PV closure. The subtle or nonfunctional nature of many of these epididymal anomalies is emphasized by the fact that PV patency per se in boys is not associated with germ cell maldevelopment or infertility.[39,40]

CLINICAL FEATURES

Many authors regard a patent PV as a potential hernia; additional factors, such as increased intra-abdominal pressure, excess peritoneal fluid, or, rarely, an underlying connective tissue deficiency, are involved in the development of a clinically apparent inguinal hernia. Consistent with the high incidence of PV patency in newborns, a hernia or hydrocele commonly manifests soon after birth and may be bilateral. Both inguinal hernias and hydroceles are more common in boys than in girls (approximately 6:1), more common on the right side (approximately 2:1), and more common in premature infants.

Typically, a hydrocele manifests as a painless scrotal swelling of variable size (Fig. 44-2) and an inguinal hernia as an intermittent inguinal swelling. A hydrocele may give a bluish discoloration to the scrotum. Hydroceles may be classified as communicating or noncommunicating, depending on the ease with which they can be decompressed by pressure, but almost all congenital hydroceles communicate with the abdominal cavity to a greater or lesser degree. Their size may vary during the course of the day, usually being smallest after a period of recumbency. The child is usually asymptomatic but may occasionally complain of discomfort in the groin or scrotum.

In older boys, a hydrocele may manifest for the first time during the course of a viral or gastroenteric illness, probably as the result of a transient excess of peritoneal fluid in the presence of a patent PV. An acute hydrocele sometimes prompts an urgent referral to the emergency department with a diagnosis of suspected testicular torsion.

Surprisingly, there is little published information on pressure measurements within hydroceles in children. A small study on a series of eight boys aged between 6 months and 3 years at the time of general anesthesia, just before operative repair, revealed hydrocele pressures of 0.5 to 16 cm H_2O (Stringer, unpublished observations, 1997-1998). A more recent study of hydrocele sac pressures in 24 boys aged between 1 and 11 years showed a median sac pressure of 11 cm H_2O (range, 3 to 30 cm H_2O).[41] Age or laterality had no significant influence on the pressure. The sac pressure exceeded the intra-abdominal pressure measured at the same time during surgery under general anesthesia in two thirds of the cases, suggesting that most hydroceles in boys are not simply the result of a freely communicating narrow-caliber patent PV. In contrast to boys, hydrostatic pressure measurements in adults with a noncommunicating hydrocele suggest that the pressure within the hydrocele always exceeds local venous pressure.[42] This may have deleterious effects on the testis.[41]

The clinical history is the key to diagnosis, because an inguinal hernia or hydrocele may be absent at the time of physical examination, especially in infants. On examination of a visible hydrocele, it is usually possible to get above the scrotal swelling and palpate the cord structures against the pubic tubercle. The cord may feel thickened (the *silk glove sign*), but clinical confirmation of a patent PV in the absence of a visible inguinal hernia or hydrocele is highly inaccurate.[43] Hydroceles are nontender and cystic in nature and may be lax or tense. In large, tense hydroceles, the testis may be impalpable, although it may be located by transillumination. If there is clinical uncertainty regarding the normality of the underlying testis, or if the testis is impalpable, ultrasound imaging is advisable.

Hydroceles characteristically transilluminate, although this is not a pathognomonic feature, and occasionally an obstructed, fluid-filled loop of bowel or even a testicular teratoma[44] may also give this appearance. Most hydroceles are readily distinguished from an inguinal hernia, but in some infants this can be difficult. If the hernial orifice is plugged with omentum or with a Richter hernia, there is frequently a distal hydrocele, and the hernia may be overlooked. In this circumstance, palpation of the internal inguinal ring by high rectal examination may help to exclude an incarcerated inguinal hernia,[45] but even this assessment is not always definitive.

Occasionally, a patent PV undergoes partial obliteration, giving rise to an *encysted hydrocele*. An encysted hydrocele may occur anywhere along the line of the PV. In the spermatic cord, it manifests as a painless, mobile, cystic swelling. It is not reducible and may occasionally be indistinguishable from an irreducible inguinal hernia. An ultrasound scan can be helpful for differential diagnosis in such cases. The sonogram typically shows an anechoic, fluid-filled structure displacing the testis and epididymis inferiorly and without any communication with the peritoneal cavity; septa may be seen occasionally, but no bowel loops should be visualized.[46]

Table 44-1 Scrotal Pathology Secondary to Intra-abdominal Disease in the Presence of a Patent Processus Vaginalis

Content of Hydrocele	Primary Pathology	Reference Nos.
Meconium	Antenatal intestinal perforation with meconium peritonitis	47, 48
Pus	Perforated acute appendicitis	49-51
Hematocele	Blunt intra-abdominal solid organ injury	52
Cerebrospinal fluid	Ventriculoperitoneal shunts for hydrocephalus	25, 53-55
Peritoneal dialysate	Peritoneal dialysis for renal failure	56, 57
Bile	Biliary ascites	58
Chyle	Chylous ascites	—
Urine	Urinary ascites	—
Air	Intestinal perforation	59, 60
Malignant tumor	Intra-abdominal malignancy	61
Splenic tissue	Splenogonadal fusion	62

ATYPICAL PRESENTATIONS

Because the patent PV is an extension of the peritoneal cavity into the scrotum, a variety of intra-abdominal pathologies may manifest with or be accompanied by scrotal signs (Table 44-1 and Fig. 44-3).[25,47-62]

A meconium hydrocele resulting from in utero perforation of the bowel is typically lax at birth. The infant may have no gastrointestinal symptoms if the perforation has healed. Meconium induces an inflammatory reaction, and the hydrocele tends to harden and may become calcified in the neonatal period.[48] The presence of abdominal calcification on the plain abdominal radiograph and hyperechogenic areas on scrotal ultrasonography should establish the diagnosis in most cases.

A hydrocele has been described as the presenting feature of acute appendicitis, with or without perforation.[49-51] Rarely, a suppurative hydrocele complicates the postoperative course of a child with generalized peritonitis; early exploration in such cases may prevent testicular loss.[50,51] Idiopathic neonatal pyocele has been described and may be mistaken for testicular torsion.[63] Hematoceles may occur secondary to intra-abdominal bleeding, such as after blunt abdominal trauma with splenic rupture,[52] or secondary to scrotal trauma. There is one report of a newborn with a hematocele secondary to adrenal hemorrhage.[64] Very rarely, a patent PV can be the conduit for metastatic spread from intra-abdominal malignancy. For example, paratesticular Wilms' tumor metastasis has been described.[61] Tuberculosis of the sac may develop in association with tuberculous peritonitis.[29]

A variety of structures can become incarcerated within an inguinal hernia, including intestine (small bowel, large bowel, appendix, Meckel's diverticulum), uterine adnexa, omentum, bladder, and an intra-abdominal catheter.[55] In splenogonadal fusion, the PV contains splenic tissue. This congenital anomaly is seen more often in boys and typically affects the left side.

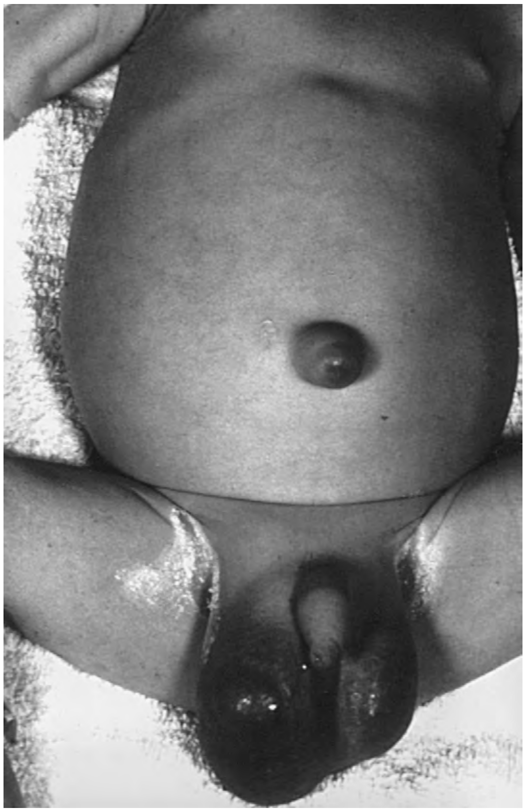

Figure 44-3 A 5-week-old infant with bile staining of the umbilicus and scrotum. Biliary ascites secondary to spontaneous perforation of the bile ducts had accumulated within hydrocele sacs. (From Howard ER, Johnston DI, Mowat AP. Spontaneous perforation of the common bile duct in infants. *Arch Dis Child.* 1976;51:883.)

It is the result of adherence of the developing spleen and gonad. In such cases, the spleen may be connected to the gonad by a cord of fibrous or splenic tissue running through the PV.[62]

A patent PV per se is rarely the cause of serious pathology. There have been a few case reports of benign and malignant mesothelioma of the tunica vaginalis (the distal part of the PV) in boys, most having presented with a hydrocele.[65,66]

MANAGEMENT

The natural history of the patent PV indicates that spontaneous closure is uncommon after the age of 2 years.[27] This is the rationale for advocating surgical repair of a hydrocele that persists or is detected after this age. Early surgery is indicated if there is suspicion of a concomitant inguinal hernia or underlying testicular pathology.

Surgical treatment consists of high ligation of the PV and partial excision of the distal sac. The operation is usually performed as an elective day-case procedure under general anesthesia. Effective postoperative analgesia may be achieved by caudal or inguinal infiltration of a long-acting local anesthetic such as bupivacaine.

Operative Procedure

The operative procedure is shown in Figure 44-4. After antiseptic skin preparation and draping of the child in a supine position, a short incision is deepened through Scarpa fascia, the external oblique is identified, and a "window" is created in the external oblique in the line of its aponeurotic fibers to expose the inguinal canal. The spermatic cord is identified, and gentle separation of the cremaster muscle fibers with a hemostat reveals the patent PV lying anterosuperiorly. After the processus is grasped, the vas and vessels are gently teased off the sac, which is then divided. The proximal processus is transfixed and doubly ligated at the internal ring with an absorbable suture (polyglactin or polydioxanone), and the redundant proximal sac is excised. The hydrocele fluid is drained via the distal sac, which is left open. The wound is closed in layers, and the skin is closed with fine subcuticular sutures. The ipsilateral testis is gently milked into the bottom of the scrotum at the end of the operation, and its position is documented. Some surgeons prefer to identify and ligate the PV outside the external ring in infants, but this may not achieve as high a ligation as the procedure described.

Postoperatively, the child is allowed to eat and drink after recovery from the anesthetic and is discharged home with simple analgesics. Return to normal activity is largely dictated by the child, but limitation of vigorous activity for 48 hours after the operation is advisable.

Routine histopathologic evaluation of the inguinal hernia sac and patent PV is common in North America but rarely performed in the United Kingdom. Supporters of this practice cite the unexpected presence of the vas deferens (0.14%) and epididymis (0.25%) in a small proportion of samples as a reason for continuing audit.[67] Others have argued that routine evaluation is not economically justifiable.[68,69]

Laparoscopy can be used to assess the patency of the contralateral PV and repair an open internal ring, if present.[70-72] This technique is most useful in cases of suspected bilateral inguinal hernia. A periumbilical cannula is inserted with the use of an open technique, a pneumoperitoneum (maximum pressure, 10 mm Hg) is created, and a 3-mm telescope is introduced. A 3-mm needle driver and 3-mm forceps are inserted in the right and left flanks, respectively, without ports. The open internal ring on the side of the hernia is closed with a purse-string or Z-type suture of absorbable or nonabsorbable material. The forceps elevate the peritoneum so that the suture does not injure the vas or vessels. The contralateral ring is inspected and considered patent if it is wider than the tip of the 3-mm forceps. A patent ring is closed with a suture.

Postoperative Complications and Follow-up

Complications after PV ligation are rare. They are similar to but less frequent than those encountered after inguinal herniotomy, which were comprehensively reviewed by Parkinson and Pierro in 2006.[73]

Early complications include local edema, hematoma, and wound infection. The potential space left by the distal PV sac may fill with fluid, giving the false impression of early recurrence. In our experience, this is rare except after inguinal herniotomy in small infants. In a prospective study of 29 baby boys weighing less than 3 kg at the time of inguinal herniotomy, five ipsilateral hydroceles were recorded in the first 2 months after surgery (representing 11% of 46 herniotomies). Two of these patients underwent a negative inguinal exploration to exclude a residual patent PV, one of the hydroceles was aspirated without recurrence, and the other two resolved spontaneously.[74]

Late complications include those related to unrecognized intraoperative problems, including recurrent hydrocele, iatrogenic upward displacement of the testis, injury to the vas deferens, and testicular atrophy. The incidence of these complications has been well documented after inguinal

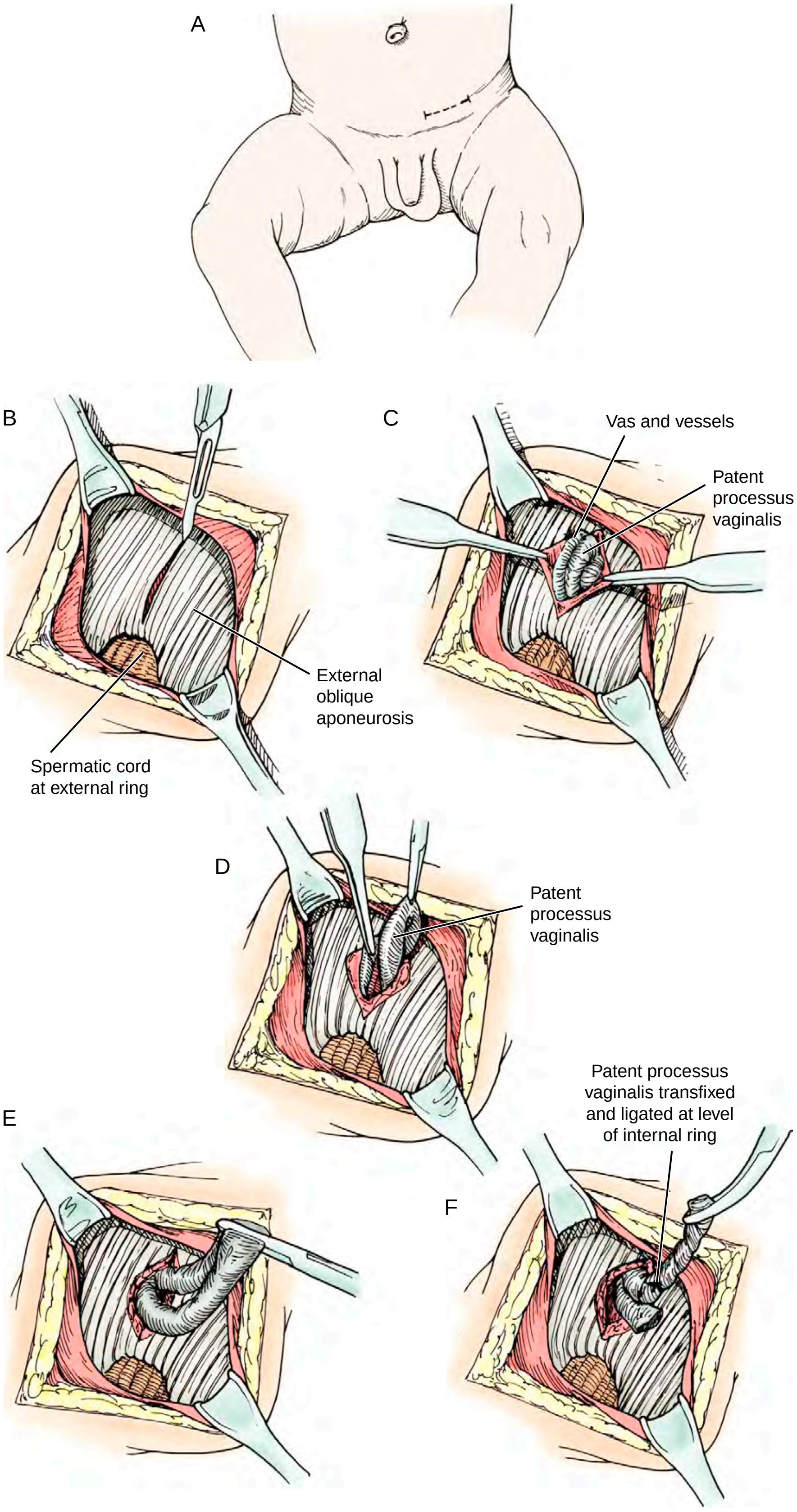
A
B
Spermatic cord at external ring
External oblique aponeurosis
C
Vas and vessels
Patent processus vaginalis
D
Patent processus vaginalis
E
F
Patent processus vaginalis transfixed and ligated at level of internal ring

Figure 44-4 Ligation of patent processus vaginalis. **A,** A skin crease inguinal incision is made to expose the external oblique aponeurosis. **B,** The external oblique is incised above the inguinal ligament and lateral to the external ring. **C,** The spermatic cord is identified in the inguinal canal. Cremasteric muscle fibers are separated from the cord to expose the patent processus, vas, and vessels. The processus is gently teased off adjacent cord structures **(D)** and divided between hemostats **(E). F,** The processus is freed proximally as far as the internal ring, where it is doubly ligated, and redundant tissue is excised. The distal processus is left open.

herniotomy,[73] and each is probably less than 1% after PV ligation. A recurrent hydrocele that persists is probably the result of failure to dissect a complete processus, tearing of a friable sac, or a slipped ligature. The groin should be re-explored, with a scrotal procedure reserved for cases in which this exploration is negative or if there is a further recurrence.

The recurrence rate after laparoscopic repair of an inguinal hernia in children is reported to be higher than after open surgery in some series; a three-center experience with 933 laparoscopic repairs yielded a 3.4% recurrence rate during a follow-up period of up to 7 years,[75] compared with a rate of 1% after open surgery.[73] Recurrence rates are higher after neonatal repair.[76] Intraoperative complications such as visceral injury or bleeding may arise from the insertion of trocars or instruments during laparoscopic repair. Port site herniation has also been described.

In the United Kingdom, the value of routine follow-up after PV ligation has been questioned.[77] In a series of 386 boys who underwent inguinal herniotomy or PV ligation, 83% attended a follow-up appointment 6 weeks later. After a total of 440 outpatient appointments, only 8 boys (1.8%) were found to have a significant abnormality (testicular malposition in 4, contralateral inguinal hernia in 4). A similar proportion of boys who were not offered routine review were subsequently referred back by their family doctor for similar problems. Early routine follow-up appears to be inefficient and not cost-effective. Two studies from North America supported this conclusion.[78,79] In one of these, a randomized trial of routine outpatient follow-up at 4 weeks after operation was compared with no routine visit; parents were equally reassured by clear verbal and written postoperative advice.[79]

Contralateral Groin Exploration

The need for contralateral groin exploration in the child with a clinically diagnosed unilateral inguinal hernia has been debated for more than 50 years and remains controversial.[80-83] There are two fundamental issues: the incidence of a contralateral patent PV and its clinical significance.

The incidence of contralateral PV patency in a child with a unilateral inguinal hernia decreases with age, as noted previously. Surana and Puri demonstrated that 50% of their patients younger than 2 years of age undergoing surgery for a unilateral inguinal hernia had a patent contralateral PV determined by surgical exploration.[82] However, only 10% of a similar cohort of patients who did not undergo routine exploration subsequently developed a contralateral hernia during a follow-up period of at least 6 years. A 1998 meta-analysis by Miltenburg and associates showed that 39% of children with a unilateral inguinal hernia had a contralateral patent PV if assessed by laparoscopy.[84] Using pooled data from more than 15,000 children, the risk of a metachronous hernia was found to be 10% among children younger than 2 years of age.[85] These studies imply that a contralateral patent PV detected in a small child at the time of unilateral inguinal herniotomy does not necessarily lead to the later development of an inguinal hernia. Clearly, careful long-term follow-up is required to determine whether the lifetime risk of a hernia or hydrocele remains at a similar low level, particularly because other studies have suggested that the lifetime risk of a contralateral hernia is as high as 30%.[81] Even using the latter figure however, routine contralateral exploration would be unnecessary in 70% of children with a unilateral inguinal hernia. Surana and Puri found that the risk of a contralateral hernia was unrelated to age (in children younger than 2 years) or to gender but was significantly greater for those presenting with a left-sided inguinal hernia.[82,83]

The benefits of routine contralateral groin exploration must be balanced against potential risks. Proponents of routine bilateral exploration argue that it may prevent a second anesthetic and operative procedure and avoid the risk of a strangulated hernia should the contralateral patent PV become symptomatic.[80,86] Those against routine contralateral exploration maintain that the cumulative incidence of a contralateral inguinal hernia is generally no more than 20%,[27] so most contralateral procedures are unnecessary.[81,83,85,87,88] Furthermore, there is a small but definite risk of injury to the vas and vessels and a subsequent risk of infertility.[81-83,89] The reported incidence of testicular atrophy after hernia repair is 1% to 2%.[81,82,89]

A 2005 survey of pediatric surgical members of the American Academy of Pediatrics found that 44% of respondents routinely explored contralateral groins in boys 2 years or younger who present with a unilateral inguinal hernia.[90] The corresponding figure for girls was 47%. This represented a decline in the proportion of respondents who performed routine contralateral inguinal exploration since a previous survey a decade earlier.

Historically, various techniques have been described to detect a patent PV. These have included surgical exploration,[27,80,82] intraperitoneal injection of technetium 99m radioisotope (in adults),[91] diagnostic pneumoperitoneum,[92] herniography,[93,94] ultrasonography,[95] and laparoscopy.[70,84,96,97] During the last 15 years, diagnostic laparoscopy has been increasingly used as a method of evaluating the contralateral internal inguinal ring for the presence of an indirect hernia or a patent PV.[84,90,98-100] In addition, laparoscopic hernia repair has been shown to be safe and reproducible.[75] This has re-energized the debate about contralateral repair of a patent PV to prevent the development of a metachronous inguinal hernia or hydrocele, particularly because the risk of inadvertent injury to the vas or spermatic vessels may be less with laparoscopic repair.

Sclerotherapy

Obliteration of a hydrocele through the injection of a sclerosant such as tetracycline is a moderately effective and well-described technique for the treatment of hydroceles in older adults.[101,102] However, because of the communicating nature of congenital hydroceles, uncertainty about the potential long-term hazards of sclerotherapy at this site (including the potential for epididymitis and infertility), the specific hazards of tetracycline in children, and the fact that some adults experience pain for several days after such treatment, there has been a justifiable reluctance to adopt this approach in children. Recurrence is more common after sclerotherapy than after operative repair.

The considerable advances in understanding of the natural process of occlusion of the patent PV made by Hutson and colleagues may yield nonoperative therapies in the future.[36]

SPECIAL CONSIDERATIONS

Ventriculoperitoneal Shunts

In most children with hydrocephalus, a ventriculoperitoneal shunt is inserted to divert cerebrospinal fluid into the peritoneal cavity. These shunts are frequently associated with the development of a hydrocele or inguinal hernia.[25,53,54] The reported incidence of this complication is about 15% to 20%, and it occurs more commonly in infants. Increased intraperitoneal fluid, a raised intra-abdominal pressure, and changes in the absorption characteristics of the peritoneum due to the effects of cerebrospinal fluid in conjunction with a patent PV have been implicated in the pathogenesis of this complication.[54,55] The hydrocele or hernia is frequently bilateral, particularly in premature infants,[25] and it may develop within days of the shunt operation, although it more commonly manifests a few months later.[53,55] Occasionally, the tip of the peritoneal catheter migrates into the scrotum through the patent PV.[55] Once the condition is diagnosed, prompt surgical repair is advisable to avoid complications related to the hernia. The surgeon should be aware of the possibility that the catheter tip may be lying within the hernia sac and of the need for a meticulous closure of the hernial sac. Contralateral inguinal exploration is advisable in these patients because of the high incidence of bilateral hernias or hydroceles.[25,53]

Peritoneal Dialysis

Chronic peritoneal dialysis is an effective and popular alternative to hemodialysis in the management of end-stage renal disease. The technique has been progressively adapted for use in smaller children, and inguinal hernias and hydroceles are a recognized complication of therapy in such cases. Between 20% and 37% of children develop an inguinal hernia or hydrocele soon after insertion of a peritoneal dialysis catheter[57,103-106]; this complication is most common in male infants. Pathogenesis is related to a patent PV in combination with the high volumes of dialysate leading to raised intra-abdominal pressure.[107]

Some authors have recommended prophylactic bilateral groin exploration and ligation of a patent PV in male infants at the time of insertion of the peritoneal catheter[56]; others have performed prophylactic ligation of any patent PV identified at peritoneography carried out after insertion of the catheter.[104] Meticulous operative repair is required in those patients who present after commencing peritoneal dialysis, once any life-threatening problems have resolved. Although most surgeons perform a standard PV ligation, some have advocated a more formal inguinal canal repair to avoid recurrence.[105] The use of small volumes of dialysate for 2 or 3 days after surgery may help to reduce the chance of recurrence.

Abdominoscrotal Hydrocele

Although this condition was first described by Dupuytren in 1834, it was Bickle in 1919 who coined the term *abdominoscrotal hydrocele*.[108] Syme is credited with the first reported case in a child, in 1861.[109]

This variety of hydrocele is rare in children, accounting for 1% of all pediatric hydroceles in one study.[110] It occurs most often in infants and is usually unilateral, although bilateral cases have been documented.[111,112] There is a scrotal hydrocele with a dumbbell-shaped extension through the deep ring into the abdomen that forms an intra-abdominal cystic mass (Fig. 44-5). The clinical picture is usually that of a boy with a pre-existing scrotal hydrocele who develops an abdominal mass. Rarely, the hydrocele is present at birth.[113] The child may be asymptomatic, but if the hydrocele becomes infected it may mimic a strangulated inguinal hernia.[114] A clinical diagnosis is possible if cross-fluctuation can be demonstrated between the intra-abdominal and the scrotal components of the hydrocele. Ultrasonography is particularly valuable and reveals a cystic, unilocular abdominal mass in continuity with the scrotal hydrocele. If the diagnosis is still in doubt, magnetic resonance imaging clearly defines the lesion.[115]

Several theories have been suggested to explain the pathogenesis of abdominoscrotal hydroceles, which may be different in children than in adults.[116-118] They include (1) intra-abdominal herniation of the inguinoscrotal hydrocele as a result of upward distention and back-pressure along the inguinal canal, (2) a patent PV with a one-way valve mechanism that allows scrotal fluid to be directed into the abdominal extension, and (3) accumulation of fluid in a congenitally preformed processus sac that has an intra-abdominal diverticulum. There is disagreement in the literature regarding the patency of the PV in these cases; some authors have commented on the absence of a residual patent PV,[112,113,119] thereby dismissing the second theory, whereas others maintain that the PV is patent.[110] The abdominal component of the hydrocele can be preperitoneal or retroperitoneal.[111,116]

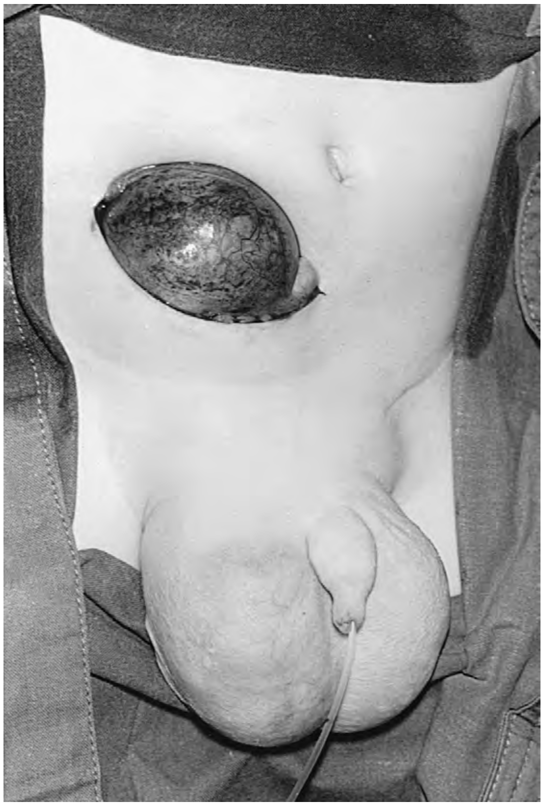

Figure 44-5 Abdominoscrotal hydrocele. (Courtesy of Mr. B. R. Squire.)

Complications have been described, including hydroureteronephrosis,[120] unilateral leg edema,[115] hemorrhage into the lesion,[121] testicular maldescent,[110,113] malignant mesothelioma of the tunica vaginalis associated with an intra-abdominal testis,[65] and dysmorphic testes.[110,122]

Spontaneous resolution does not occur, and surgery is the treatment of choice. Complete excision of the sac with reconstruction of the inguinal canal is the aim and may be accomplished via an extended inguinal incision. Dissection is often facilitated by preliminary aspiration of the hydrocele. The dissection can be difficult if the sac is very adherent to cord structures, and careful hemostasis is required.[114] A laparoscopic approach to this pathology has been described.[123] The advantages of this technique include minimal groin dissection, laparoscopic mobilization of the retroperitoneal abdominal component (Fig. 44-6), and excellent visualization of the cord structures. The hydrocele sac can be finally removed through a small groin incision.

Ascending Testis

The ascent of the testis from a normally descended scrotal position to an undescended position was first described by Villumsen and Zachau-Christiansen in 1966.[124] In 1985, Atwell

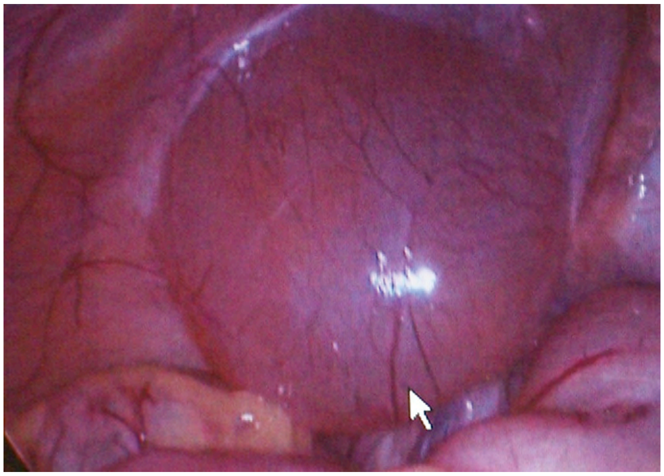

Figure 44-6 Laparoscopic view of the abdominal component of a left-sided abdominoscrotal hydrocele *(arrow)*.

reported on 10 children in whom ascent of the testis was carefully documented.[125] In nine of these children, a complete hernial sac was found at the time of orchiopexy, which was undertaken at a mean age of 9.4 years. None of the boys had a clinically apparent inguinal hernia. Atwell proposed that the absence of complete regression of the PV leaves a fibrous and nonelastic tissue in its place. This vestigial structure may prevent elongation of the spermatic cord in response to somatic growth, thereby anchoring the testis, which would then assume a higher position.[125] Alteration in the length of the inguinal canal with growth was postulated as an additional factor. Subsequent reports have supported the concept of the ascending testis,[126-128] but some authors have suggested that adhesions surrounding a retractile testis might explain some cases.

A prospective study of boys with acquired undescended testes showed that the majority experienced spontaneous testicular descent after puberty; fewer than 20% required an orchidopexy.[129] Reassuringly, histopathologic studies on testicular biopsy specimens obtained at orchidopexy have shown no significant differences between ascended testis and normally descended testis.[130]

CONCLUSION

The development of the PV is related to the descent of the testis. In most boys, the processus is patent at birth and closes spontaneously during childhood. The molecular mechanisms responsible for closure are gradually being unraveled. Persistence of a patent PV can lead to the development of a hydrocele or inguinal hernia. Rarely, scrotal pathology can be an early manifestation of intra-abdominal disease as a result of a patent PV. Ongoing controversies in the management of the PV include the role of laparoscopy and the need for contralateral groin exploration to identify and repair an asymptomatic patent PV in a child with a unilateral inguinal hernia or hydrocele.

REFERENCES

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CHAPTER 45

THE PEDIATRIC VARICOCELE

Paul Zelkovic and Stanley J. Kogan

As recently as 1970, pediatric varicoceles were considered to be unimportant. Major changes in management occurred in 1974, coincidental with publication of *Dialogues in Pediatric Urology,* which contained an article entitled, "Pediatric varicoceles: changing concepts."[1] In this article, it was noted that pediatric varicoceles occur much more frequently than was previously recognized; that some boys with pediatric varicocele have a clear-cut reduction in ipsilateral testicular volume; that pediatric varicocele is, in all likelihood, the cause of the small testis seen in grown men with varicocele and subfertility; and that varicocele correction in childhood can result in "catch-up" growth of the involved testis in the majority of boys undergoing surgical repair.[1] Since then, a plethora of new knowledge has supported and further expanded these concepts.

In this chapter, information pertinent to the natural history of untreated and treated pediatric varicoceles is reviewed, current controversies regarding varicocele management are recounted, and the various treatments available and their results are described.

INCIDENCE

Varicoceles occur more commonly in adolescent boys than was previously suspected. Various studies indicate an approximate frequency of 16% (Table 45-1). Clinical observation indicates that puberty-associated testicular enlargement, with its concomitant increased blood flow, is the factor causing most varicoceles to appear. Screening studies demonstrate a paucity of varicoceles in prepubertal boys, with a significant progressive increase in frequency as puberty progresses. The incidence of pediatric varicocele may actually be underestimated, because many varicoceles either are not detected by primary care doctors and are discovered later in adult infertility clinics or never materialize as fertility problems and are not reported. Pediatric varicoceles are often associated with a unique body habitus: Various studies have demonstrated a clear association with increased height and weight and lower than normal body mass index in adolescent boys and adult men with varicocele.[2-5] Varicocele frequency appears to be prevalent in first-degree relatives of index patients with varicocele. One study demonstrated a 56.5% prevalence of varicocele among first-degree relatives of adult male varicocele patients (as determined by physical examination), with the highest frequency among the sons of fathers with varicocele (67%).[6]

Studies in adults show that between 80% and 90% of varicoceles occur on the left side. Right-sided varicoceles are uncommon, are usually noted only when bilateral varicoceles are present, and seldom occur as an isolated finding. These observations hold true for pediatric varicoceles as well, although new information indicates that subtle right varicocele may coexist with clinical left varicocele far more frequently than previously described (see later discussion).

ANATOMY AND PATHOPHYSIOLOGY

The arterial and venous anatomy of the testes has been studied in great detail and is well described elsewhere.[7,8] Briefly stated, there is a tripartite vascular supply to the testis consisting of the internal spermatic (testicular) artery and vein, the latter of which drains into the renal vein on the left side; the vasal artery and vein, which drains via the inferior vesical vein into the hypogastric vein; and the cremasteric artery and vein, which drains via the inferior epigastric vein into the external iliac vein (Fig. 45-1). There is free communication between the arteries at the testicular level as well as between the veins that form the pampiniform plexus. The distal part of the pampiniform plexus is drained via the anterior scrotal vein into the femoral vein.

As the venous plexus extends up the spermatic cord out of the scrotum, adjacent arterial blood is cooled from 37° C to 33° C, the temperature of scrotal venous blood, by a countercurrent heat-exchange process.[9] This process takes place bilaterally, and when a varicocele forms, current theories indicate that the heat-exchange process is disrupted, increasing arterial and testicular temperatures as well as testicular blood flow. Because local scrotal, inguinal, and pelvic cross-collaterals exist, the temperature in both testes is affected even though the varicocele is present on only one side (Fig. 45-2). When testicular temperature is increased, a multitude of data indicate that the testis is adversely affected in a variety of ways. These processes are best described cumulatively as producing the *varicocele effect*.

Although numerous other conditions, such as incompetence of the internal spermatic vein due to absent valves, retrograde flow of toxic metabolites from the adrenal gland, increased venous pressure, and compression of the renal vein by the superior mesenteric artery ("nutcracker" phenomenon),[10] have been postulated historically as causes of the varicocele effect, none fully explains the detrimental effect varicoceles have on testis function and fertility. Countercurrent heat-exchange disruption seems to be the most plausible theory, and it readily explains other aspects of the varicocele effect.

*Ipsilateral testis growth arrest** is noted in 25% to 75% of boys with varicocele.[11,12] This finding may not be apparent at initial examination, but as puberty progresses, an increasing number of boys are found to have a smaller than normal testis.[13,14] Published studies are at variance regarding the risk of growth arrest related to varicocele grade, some indicating that it occurs with equal frequency in each grade[15] and others demonstrating an increased frequency with increasing varicocele grade.[16] Larger varicoceles may also be associated with volume loss of the right testicle as well as the left.[17] Growth arrest is often associated with a softer testis as well.

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*In this chapter, the term "growth arrest" is used to describe more accurately the smaller testis associated with the varicocele rather than "atrophy," which suggests shrinkage from an already normally achieved size.

Table 45-1 Frequency of Varicocele in Adolescent Boys

Study	*n*	Age Range (yr)	Frequency (%)
Horner, 1960[59]	1211	11-16	15.9
Oster, 1971[60]	837	10-19	16.2
Steeno et al, 1976[32]	407	12-25	14.7
Yerokhin, 1979[61]	10,000	10-17	12.4
Berger, 1980[62]	586	10-17	9.0
D'Ottavio, 1981[63]	5177	11-16	25.8
Total	21,878		16.3

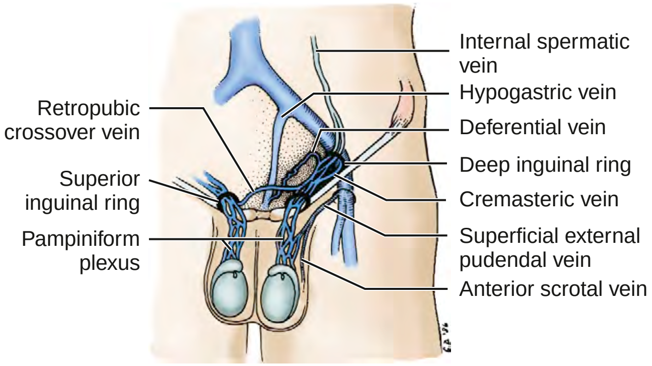

Figure 45-1 Venous drainage of the left testis. (From Levitt SB, Gill B, Katlowitz N, et al. Routine intraoperative post-ligation venography in the treatment of the pediatric varicocele. *J Urol.* 1987;137:716-718.)

Histological abnormalities have been described in some biopsy specimens taken at the time of varicocele repair. These changes may affect all cellular compartments within the testis; germ cell maturational arrest and sloughing, ultrastructural changes in the Sertoli cells, and alterations in the Leydig cells ranging from atrophy to hyperplasia have been described.[18,19] Leydig cell histology has been shown to have a prognostic value; for example, those varicocele patients who had severe Leydig cell atrophy were also found to have high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and low testosterone levels. Successful varicocelectomy failed to increase sperm counts in these patients. Degenerative alterations in the venules and capillaries exist as well; they consist of endothelial proliferation and basement membrane thickening and may be observed before significant changes are seen in the testicular tubules. These latter changes in the vessels and Leydig cells are considered to be significant in the pathogenesis of the varicocele effect, ultimately affecting germ cell production and fertility. Importantly, there is a spectrum of abnormalities, varying from individual to individual, so the degree of damage in any individual case cannot be stated with certainty without a biopsy.[20]

On a *biochemical cellular level*, experimental animal data and data from adults with varicocele indicate that the intratesticular testosterone concentration is diminished in varicocele-associated testes.[21] Age-related decreases in serum testosterone levels are noted in some patients with varicocele as well.[22] Because testosterone is necessary for normal spermatogenesis, these findings correlate well with the impaired spermatogenesis seen in some varicocele patients and with the Leydig cell ultrastructural changes described.[19,21] Serum inhibin B levels have also been measured in adolescents and adults with varicocele.[23,24] Inhibin B is a glycoprotein produced by Sertoli cells that may be considered as a marker of Sertoli cell function, with reduced levels noted in various testicular conditions associated with Sertoli cell dysfunction. Serum inhibin B is believed to interact in the "short-loop" feedback controlling serum FSH levels, so that altered Sertoli cell function is associated with reduced serum inhibin B levels and increased FSH levels in some patients. In one study of nine pubertal boys with varicocele, serum inhibin B levels were normal in boys with both normal and diminished-size testes.[23]

The important net result of these findings associated with the varicocele effect is that spermatogenesis is impaired in many adults and in a number of adolescents with varicocele. Because semen analysis is not routinely determined in adolescents undergoing varicocele evaluation, the few studies in which semen analysis has been done should be scrutinized carefully to enhance our understanding of the early process. In one, 67 adolescent males aged 17 to 20 years with varicocele underwent varicocelectomy or observation, and a group of healthy adolescents without varicocele were used as controls. No differences in semen parameters were noted initially, but after 1 year, the sperm concentration was significantly higher in the treated group.[25] In another study, 88 adolescents with moderate or large varicocele were contrasted with 21 control patients: The total sperm number was statistically diminished in those with a reduced testis volume.[13] In another study in which semen analysis was performed after 1 year in pubertal adolescents with varicocele who underwent observation versus repair, statistically significant differences in sperm density, motility, and morphology were noted.[26] Normal semen parameters were noted in only 20% of the uncorrected group. These findings indicate that adverse testicular changes which in all likelihood affect later fertility do occur early on, at least in some adolescents with varicocele, and this information

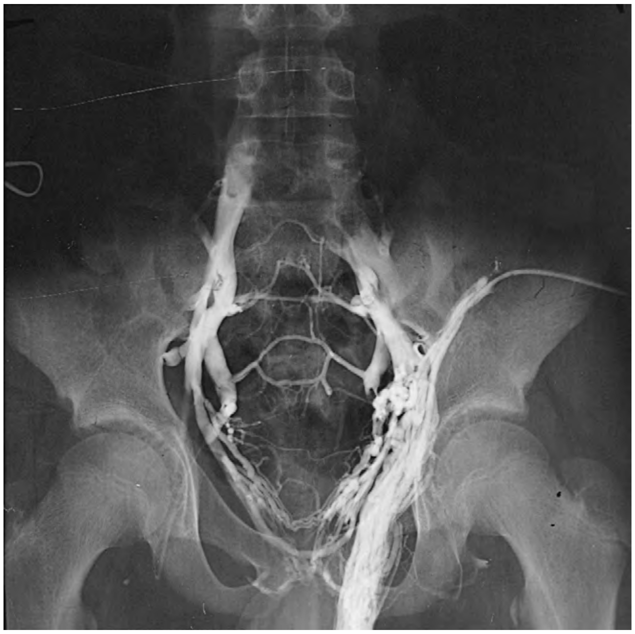

Figure 45-2 Intraoperative left spermatic venogram demonstrates a varicocele and crossover pelvic venous collaterals draining to the right internal iliac vein.

should significantly affect decisions regarding management and treatment.

DIAGNOSIS

The majority of pediatric varicoceles are asymptomatic, manifesting as a scrotal swelling discovered during routine physical examination. A minority are discovered by the patient in the same manner or because of a dull, nagging ache in the scrotum. It is imperative that the examination to detect a varicocele be done with the patient in an upright standing position, because the dilated veins will collapse when the patient lies down and even a large varicocele will remain undetected if the patient is not upright. A Valsalva maneuver should be requested (cough or abdominal straining or both); this will produce a "tapping" sensation, representing transmission of increased abdominal pressure in the scrotally palpated dilated veins.

Varicoceles are traditionally graded I through III (Table 45-2). Subclinical varicoceles (grade 0) are not recognized in general in adolescence, because there is no reason to consider their presence unless an otherwise unexplained small testis is present. Observations indicate that varicocele frequency and varicocele grade increase with progression of puberty. A larger percentage of higher-grade varicoceles occurs during later pubertal stages. When a varicocele is detected, the testis size (volume) and consistency should be noted. Orchidometry using the Prader or Takihara models should be performed, or ultrasonography may be used to more precisely define differences in size.[10] Orchidometry has been shown to provide reliable reproducibility between observers, although its sensitivity in determining testis volume differentials was found to be limited compared with ultrasound.[27,28] Testis volume may be compared with measurements in normal boys, but a more practical and useful comparison is to note size differences between the patient's own two testes (except, of course, when the contralateral testis is diseased or absent). Although minimal differences in size between the left and the right testes occur in normal individuals, data indicate that a size difference greater than 2 cm^3 should be regarded as significant and abnormal.[29] This measurement is obviously age- and pubertal-stage dependent, a 2-cm^3 size difference in an adult being less significant than the same difference noted in a prepubertal or peripubertal adolescent.

Even small varicoceles may be associated with a subfertility effect. Doppler ultrasonography is useful to detect retrograde venous reflux with a Valsalva maneuver and should be performed along with conventional morphologic imaging if there is suspicion about the diagnosis and the varicocele is difficult to feel. Ultrasonography may also prove useful occasionally in diagnosing a subclinical varicocele in a boy with an unexplained small testis and an impalpable varicocele. In these circumstances, the subclinical varicocele should be corrected because of its presumed effect on testicular growth. The significance of a subclinical varicocele detected in the absence of ipsilateral testicular growth arrest in adolescence is unclear at this time.

Other techniques for diagnosing varicocele, such as preoperative internal spermatic vein venography and scrotal thermography, have been utilized in adults. These have limited usefulness in adolescence and are not routinely utilized. Similarly, semen analysis is an integral component of varicocele evaluation in adults but is seldom utilized in adolescents because of associated anxiety regarding fertility-related issues and masturbation and because decisions regarding treatment are usually based on physical findings alone. Furthermore, normative values for semen parameters during early puberty have not been defined.

Table 45-2 **Varicocele Grading**

Grade	Description
0 (subclinical)	Not visible or palpable; identified only by ultrasound
I	Not visible; palpable in upright position with Valsalva only
II	Not visible; palpable in upright position without Valsalva
III	Visualized and palpable without Valsalva

Endocrine evaluation using measurements of serum FSH and LH levels after provocative testing with gonadotropin-releasing hormone (GnRH) has similarly been advocated in adults and adolescent boys with varicocele to identify those with testicular dysfunction. The diagnostic ability to detect testicular dysfunction in these circumstances would be especially helpful clinically, because we could then indicate which boys—even those with normal-size testes—would benefit from adolescent varicocele repair. However, data indicate that these studies are insufficiently accurate to be clinically useful. In one study of 53 adolescents (aged 11 to 17 years) with varicocele, about one third demonstrated an exaggerated FSH and LH response to GnRH stimulation. It was believed that these boys might have some element of testicular damage. Varicocele size, age, and serum testosterone levels were not significantly different between those with normal and those with abnormal GnRH responses. Most importantly, a significant number of boys with normal-size or growth-arrested testes had abnormal GnRH tests.[30] Similar findings were noted in other studies.[23,31] These data suggest that hormonal testing used in this manner is clinically unhelpful and that other means are necessary when attempting to determine which adolescents with varicocele should undergo repair.

TREATMENT

Operative versus Nonoperative Treatment

When considering the varicocele effect, it is reasonable to weigh the risks and benefits of operative versus nonoperative treatment.

Nonoperative Treatment

Data indicate that nonoperative (observant) treatment is associated with a progressive number of smaller than normal testes as puberty progresses. Testes initially determined to be equal or slightly different in size sometimes demonstrate progressive growth arrest with time. Puberty progression is also associated with an increased percentage of higher-grade varicoceles, so a direct relation exists between patient age, pubertal stage, and varicocele size, and an inverse relation occurs between varicocele size and testis size.[32] Selected studies in adolescents have also indicated that observant therapy is associated with deterioration of semen parameters in some adolescent boys with varicocele.[13,15,29,33]

These findings demonstrating progressive deterioration in semen parameters are not limited to adolescence. At least two studies in adults have demonstrated that some men with varicocele develop progressive loss of fertility with time despite normal initial fertility. In one report, 98 of 1099 subfertile men had secondary subfertility (i.e., they were fertile initially).[34]

Table 45-3 Treatment Options

Technique	Complication Rate	Cost*	Failure Rate	Comments
Conventional inguinal	3-8.6% Hydrocele	$	16% Recurrence (adolescents) 9% Recurrence (adults)	Easiest technique
Microscopic inguinal	0% Hydrocele	$$	0.6% Recurrence	Very low complication rate
Microscopic subinguinal	0.8% Hydrocele	$	2.1% Recurrence	Can be done under local anesthesia; fast recovery
Retroperitoneal	7.2% Hydrocele	$	13.6% Recurrence (adolescents, artery-sparing) <2% Recurrence (adolescents, artery taking) 15% Recurrence (adults)	Most common method of pediatric urologists
Laparoscopic	Similar to retroperitoneal	$$$	15% Recurrence	Fast recovery, but potential for serious injury
Embolization	11% Overall rate†	$$$	5% Recurrence and 27% nonocclusion rate, for a 31% overall failure rate	Fast recovery

*Relative costs estimated on necessity for anesthesia, time in operating room, and equipment.

†Most relatively minor, including extravasation, contrast reactions, pain, puncture of femoral artery, testicular thrombophlebitis.

From Skoog SJ, Roberts KP, Goldstein M, Pryor JL. The adolescent varicocele: what's new with an old problem in young patients? *Pediatrics.* 1997;100:112-121. Used with permission of the American Academy of Pediatrics.

A varicocele was detected in 35% of those with primary subfertility and in 81% of those with secondary subfertility, suggesting that the varicocele effect was progressively responsible for the loss of fertility in these men. In another study, semen analyses performed in 13 men with untreated varicocele and repeated 9 to 96 months later demonstrated significant deterioration in semen quality.[35] These findings led to the conclusion that nonoperative treatment exposes varicocele patients to the need for lifelong follow-up and the potential for progressive subfertility, even after normal fertility is present. Furthermore, it is well recognized that varicocele repair in adults is not universally successful in reversing the associated subfertility. These findings argue strongly for varicocele repair in adolescence, especially when testicular growth arrest is present.

By contrast, arguments in favor of observant (nonoperative) treatment exist, indicating that not all adolescents with varicocele suffer growth arrest of the ipsilateral testis and that not all ultimately become subfertile. Many men with untreated varicocele are fertile, at least initially. It would be helpful to avoid surgery in some patients; however, we cannot predict who will subsequently develop testicular growth arrest or who will be subfertile as an older adult.

Operative Treatment

The risks and benefits of operative treatment need to be considered as well. Varicocelectomy in childhood may, in general, be performed with minimal morbidity; however, the procedure is not without potential complications regardless of the surgical technique utilized. Hydrocele formation despite varicocele cure and varicocele persistence are the two most common complications (Table 45-3). Other complications, such as funiculitis, transient epididymitis, and testis atrophy, are exceedingly rare. Hydroceles occur as a result of lymphatic disruption at the time of venous ligation. Lymphatic-sparing techniques minimize but do not fully eliminate this risk. Hydroceles occurring in this context will eventually require repair if they undergo progressive continued enlargement.

Considerable attention has been paid to determining how hydrocele occurrence might be minimized. In a 4-year follow-up study of 278 children after varicocele repair at eight European centers, 12% had hydroceles. No difference was found between the laparoscopic versus open repairs, but hydroceles occurred more frequently when mass ligation of both the testicular artery and veins was done.[36] A 23% rate of hydrocele occurrence was described in 79 boys in whom mass ligation of both vessels was done during laparoscopic repair, which occurred three times as frequently when the vessels were divided as well as just simply ligated.[37] Bilateral repairs have also been cited as having a higher frequency of hydroceles eventually requiring surgical repair.[38] Other studies reported widely disparate results for various surgical techniques and approaches. The relative frequency of hydrocele occurrence, however, has led to approaches attempting to lessen this frequent occurrence. Intratesticular injection of isosulfan blue dye at the time of varicocelectomy was described as a means of accurately identifying and preserving spermatic cord lymphatics intraoperatively; no hydroceles occurred when this technique was used in conjunction with microsurgical preservation of the identified lymphatics.[39] These findings suggest that lymphatic- and artery-sparing techniques may optimize hydrocele prevention associated with varicocelectomy.

Varicocele recurrence (or persistence) is a most disconcerting problem; reoperation is always required, because the original condition has not been resolved. Experience indicates that persisting unrecognized veins adhering to the wall of the internal spermatic artery are the most common cause for varicocele recurrence; because these recurrences often are noted soon after surgery, we personally believe that most are in fact persistences of incompletely ligated veins rather than true later recanalizations.[8] Recurrences seem to be more common with adolescent varicocelectomy than in adults, and they are minimized by use of the operating microscope. If an open surgical technique is used, high retroperitoneal ligation appears to be more beneficial than inguinal ligation. Mass ligation of the spermatic vessels reduces recurrences, as does use of intraoperative venography (see "Controversies in Varicocele

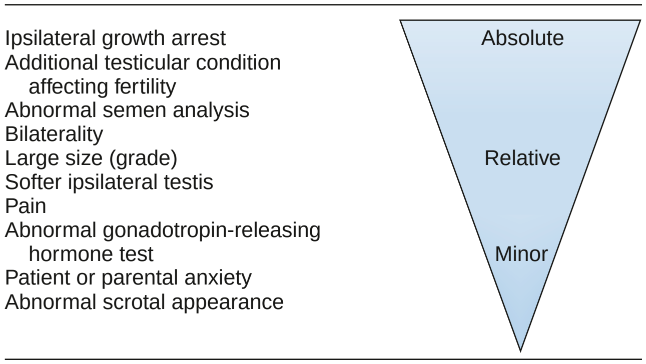
Ipsilateral growth arrest
Additional testicular condition affecting fertility
Abnormal semen analysis
Bilaterality
Large size (grade)
Softer ipsilateral testis
Pain
Abnormal gonadotropin-releasing hormone test
Patient or parental anxiety
Abnormal scrotal appearance
Absolute
Relative
Minor

Figure 45-3 Absolute and relative indications for varicocelectomy in adolescents.

Management"). Laparoscopy offers the benefit of visualizing a wide local magnified surgical field, allowing for potentially improved results.

Against these risks must be weighed the obvious benefits of varicocelectomy in adolescence. Reversal of testicular growth arrest occurs in 50% to 75% of adolescents undergoing successful varicocele repair.[12,26] Semen quality has been demonstrated to improve in the few cases in which it has been studied.[25,26] Psychological benefits accrue as well: Depression related to issues of sexuality, infertility, and body image and anxiety have been observed and reported in untreated patients.[32] There is a great psychological benefit derived in adolescence by having an illness "resolved" rather than persisting as an issue and cause for continued concern.

Indications for Treatment

Indications for varicocelectomy in adolescents differ from those in adults, in whom the procedure is done mostly for infertility-related reasons. The observations that a number of adolescents with varicocele will present with or subsequently develop testicular growth arrest, that these constitute the body of those adults with small ipsilateral testes and infertility later in life, and that varicocelectomy in adolescence can predictably reverse testicular growth arrest in the majority of boys all offer significant justification for performing varicocelectomy in adolescence. However, because not all boys with varicocele will ultimately suffer from subfertility as adults, some selectivity is in order. Prophylactic varicocelectomy in all adolescents with varicocele would represent an extreme position.

In an effort to better define the indications for performing varicocelectomy in adolescence, a relative scale of indications has been derived (Fig. 45-3). The only absolute indication universally agreed on is a significantly smaller ipsilateral testis. The implications of other indications should be discussed fully with the parents and, when appropriate, with the patient, so that a fully informed decision regarding the benefits and risks of surgery may be arrived at.

Surgical Techniques

Multiple techniques for treating varicoceles in adults have been described, and all are frequently used for pediatric varicoceles as well. Retrograde femoral vein catheterization with embolization or sclerotherapy has found only limited appeal among pediatric urologists. Until recently, conventional treatment consisting of transinguinal or suprainguinal open surgical repair was used exclusively. With the popularization of microsurgical varicocelectomy and laparoscopic varicocelectomy in adults, these techniques have also been used in adolescents.

Open Transinguinal Repair

Open transinguinal repair (Ivanissevich repair) consists of opening the inguinal canal in standard fashion, mobilizing the entire spermatic cord and then carefully identifying and ligating the offending varicosities, which at this inguinal level are usually multiple. Placing the patient in reverse Trendelenburg position and using optical loupe magnification help in identifying the dilated veins. The artery is identified and preserved, although some surgeons practice mass ligation of the entire internal spermatic pedicle. In some instances when arterial identification is difficult, warm saline solution or papaverine drip directly on the vessels is helpful. Care must be taken to avoid the ilioinguinal nerve and the vas deferens and its vessels, because these vessels must remain as the main source of venous drainage for the testis after ligation. Use of intraoperative venography may aid in avoiding unrecognized "bypass collaterals," which would result in a persistent varicocele. (See section on the role of venography.)

Open Repair with High Retroperitoneal Exposure

Use of an open high retroperitoneal (Palomo) exposure offers advantages over the transinguinal route. The incompetent internal spermatic veins are more often single, and the exposure is above the vas deferens and its accompanying vessels, thereby avoiding them completely. A transverse abdominal incision is made 1 to 2 fingerbreadths medial to the anterior superior iliac spine and the same distance above the estimated position of the internal inguinal ring. A muscle-splitting technique is used to enter the retroperitoneum. A reverse Trendelenburg position and a slight contralateral tilt of the operating table aid in exposure, which is obtained with right-angle retractors of appropriate size. The internal spermatic vessels are identified on the posterior aspect of the peritoneum and are looped with a Penrose drain or holding sutures. This exposure can prove difficult in the obese adolescent; traction on the ipsilateral testicle often aids in identifying the elusive vessels in this circumstance. At this level, the vas and its surrounding vessels are well inferior. Ligation is performed in the manner described previously and is complemented by internal spermatic venography.

Transperitoneal Laparoscopic Repair

With the widespread use of laparoscopy, transperitoneal laparoscopic varicocelectomy has been adopted preferentially by many pediatric urologists. The advantages provided by this minimally invasive surgical route are obvious: rapid patient recovery and mobilization, minimal morbidity and pain, and rapid return to all normal activities. An additional benefit is that the technique provides a direct, magnified visualization of the internal spermatic vessels and collaterals high above the vas deferens and surrounding vessels. This approach is especially useful in the rare circumstance in which bilateral varicoceles are present. Its disadvantages are increased cost and the potential for injury of abdominal viscera and vessels resulting from trocar insertion or dissection. As with other aspects of laparoscopic surgery, evolutions in technique and instrumentation have occurred. Miniaturization of laparoscopic ports and instrumentation has lessened morbidity without compromising surgical technique and safety. Improved camera optics have significantly facilitated surgical visualization.

For transperitoneal laparoscopic repair, an incision is made at the umbilicus and deepened down to the infraumbilical midline fascia, which is incised. A vertical incision on the inferior crest of the umbilicus is used if the umbilicus is deep or a curvilinear incision following the crest if it is flat. Pneumoperitoneum is produced by Veress needle insertion while the umbilicus and abdominal wall are elevated with towel clips. Needle position is checked by the open saline solution drop and direct injection techniques. Alternatively, the dissection may be continued into the peritoneum with port insertion under direct vision. A 5-mm video port is then established. Pneumoperitoneum is established at pressures of 12 cm H_2O. A second 5-mm port is placed under direct vision in the midline just over the pubis, a position that ultimately will be hidden in the pubic hairline. A third 3-mm port is placed midway between the other ports in the midline or midway between the umbilicus and the anterior superior iliac spine, superior to the internal inguinal ring. Establishing a steep reverse Trendelenburg position and tilting the table slightly to the right facilitates retraction of the bowels. The posterior peritoneum is incised over the internal spermatic vessels with a T incision, and the spermatic veins are mobilized. A 5-mm automated clip applier is passed through the lowest port, and the veins are elevated, clipped, and divided. The venous closure device may be used through this 5-mm port as a clipless alternative. Some surgeons clip the entire arterial and venous pedicle without attempting to isolate the artery, which simplifies the procedure considerably. After reducing the pneumoperitoneum pressure and ensuring that the operative field is dry, the surgeon removes the trocars under direct vision. Fascial closure is made for the umbilical port; the 3-mm ports require skin closure only.

Preperitoneal Laparoscopic Repair

Preperitoneal laparoscopic repair offers additional benefits. In addition to the other advantages of the laparoscopic minimally invasive route, injury to the intra-abdominal contents is avoided by a preperitoneal approach, because the internal spermatic vessels are isolated extraperitoneally. After an infraumbilical incision is made in the manner described previously, a subcutaneous plane is developed over the left anterior rectus sheath, which is then incised for a short distance to the left of the midline. The left rectus muscle is retracted laterally, and a peanut dissector is passed posterior to the left rectus muscle to the level of the pubis, establishing a pathway for the 10-mm preperitoneal balloon dissector, which is then inserted and inflated manually. The preperitoneal space is developed under direct vision, using a 0-degree viewing lens. The balloon dissector is deflated and removed, after which a Hassan 10-mm port is placed and pneumopreperitoneum is established at 12 cm H_2O. Two identical ports are placed under direct vision in the midline, as described for the transperitoneal approach. The internal spermatic vessels are identified laterally, aided by traction on the testicle, which is draped into the sterile operative field. The vessels are grasped and elevated well above the vas deferens and its vessels, which can be seen coursing medially; varicocelectomy then proceeds as described for the transperitoneal laparoscopic repair (Fig. 45-4). With this technique, the risks of bowel injury and postoperative hernia are eliminated because the peritoneum is not opened, and the testicular artery can be identified and preserved in most instances. Experience within 102 boys ages 8 to 19 years demonstrated the efficacy of this technique: 2 postoperative persisting varicoceles and 1 presumed recanalization recurrence were noted 3 years after the surgery. Five boys developed hydroceles (4.9%), resulting in hydrocele repair in two.[40]

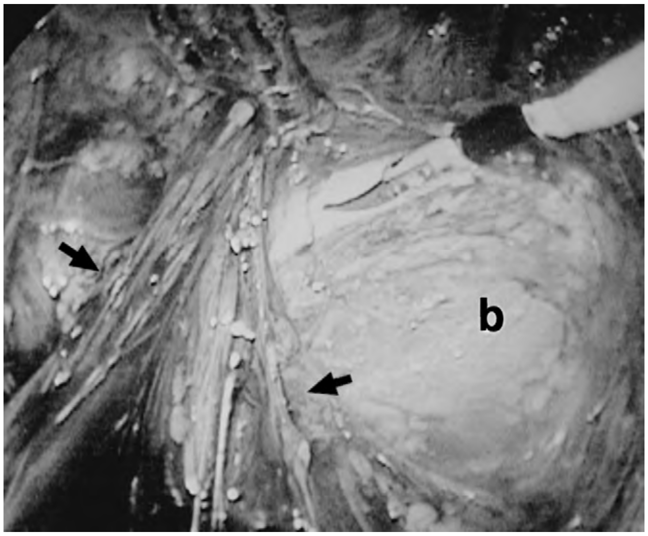

Figure 45-4 Intraoperative visualization of the internal spermatic vessels *(left arrow)*, the vas deferens *(right arrow)*, and the bladder (b) during laparoscopic preperitoneal varicocelectomy.

Angiographic Repair

Angiographic varicocelectomy has a limited usefulness in children. General anesthesia is invariably needed. These procedures are usually performed by interventional radiologists and involve the injection of various sclerosing agents or placement of occluding detachable angiographic coils or balloons to obliterate the internal spermatic veins. The occlusive agent is usually delivered by first obtaining venous access via the femoral or jugular approach. Complications in childhood include difficulty catheterizing the internal spermatic vein, extravasation of contrast material, coil migration, and a significant rate of varicocele persistence (see Table 45-3). As a result, these procedures are seldom used as primary procedures in children, but they may have a secondary role in treatment of the recalcitrant persisting varicocele, because persisting veins can be accurately studied and defined radiologically and then obliterated in the same procedure.[8,41]

Microsurgical Repair

Microsurgical varicocelectomy has distinct advantages over the other routes and has been widely adapted for adolescent varicocele repair.[42,43] A subinguinal or low transverse inguinal incision is made with isolation of the spermatic cord. The external oblique aponeurosis is opened in prepubertal boys and the cord is isolated higher up, which aids in identification of the very small testicular artery. The testis is delivered out of the scrotum, and all external spermatic veins and scrotal veins are divided. The testis is then returned to the scrotum. Under increased (6× to 25×) magnification provided by the operating microscope, all internal spermatic veins are clipped or tied and divided. The vas deferens and its vessels and the arteries and lymphatics are identified and preserved. Although this procedure may be done in adults under local anesthesia and sedation, general anesthesia is usually required in adolescents.

It has been argued that the use of approaches other than the microsurgical approach is illogical because most adult infertility surgeons are gravitating to the latter technique because of the benefits provided by significant magnification. The testicular artery diameter ranges between 0.3 mm in the peripubertal boy and approximately 1.0 mm in the adult, so the added magnification is obviously beneficial because it allows for more accurate identification of the elusive small artery and for identification and preservation of the accompanying lymphatics. Artery preservation is maximized by microsurgical varicocelectomy, and postoperative hydrocele occurrence and varicocele persistence are minimized because lymphatics and periarterial veins resulting in persistence are more easily visualized. Published results attest to the efficacy of this approach in adolescents.[42-44]

CONTROVERSIES IN VARICOCELE MANAGEMENT

Table 45-4 lists the controversies in varicocele management.

Table 45-4 Controversies in Pediatric Varicocele Management

Choice of operative technique
Safety of ligating the internal spermatic artery
Role of venography
Frequency of bilaterality
Treatment of persistent or recurrent varicoceles

Choice of Operative Technique

The choice of incision site and technique for varicocelectomy traditionally has been arbitrary, determined by the surgeon's preference without scientific basis. Logically, a high retroperitoneal approach would seem to most reliably interrupt the internal spermatic vein with the least chance for failure. However, this approach does not address pelvic or scrotal collaterals, which potentially could cause varicocele persistence. Furthermore, it does not fully eliminate persistence from the rare retroperitoneal collateral bypassing the point of higher retroperitoneal internal spermatic vein division, out of view within the limited surgical incision (Fig. 45-5). On the other hand, despite its simplicity, transinguinal varicocelectomy clearly is associated with a much higher recurrence rate owing to multiple potential sources for bypass collateral filling of the internal spermatic vein. Published data indicate that if either of these approaches is used, complementary performance of intraoperative venography lessens the risk of varicocele persistence.

If mass ligation of all veins and arteries exclusive of the vas deferens and its accompanying vessels is done, studies show that the incidence of persistence or recurrence is also lessened dramatically (see Table 45-3). Intraoperative venography does not add any additional benefit in this circumstance. However, the safety of routine testicular arterial ligation has been questioned, and added risks may accrue (see next paragraph).

Both the microsurgical low approach with delivery of the testis and the laparoscopic approach resolve some of these problems. The wider field of view provided by laparoscopy and the increased magnification provided with both of these techniques offer improvements over standard open surgical approaches.

Safety of Ligation of the Testicular Artery

Controversy is significant regarding the safety of routine ligation of the testicular artery along with the testicular veins. Arguments in favor indicate that ligation of the artery includes the tiny periarterial veins that often result in persistence of the varicocele and leads to a significantly diminished recurrence rate. In one series, there was an 11% recurrence rate with artery-sparing varicocelectomy in adolescence versus 1.3% with mass ligation including the artery[45]; a later report

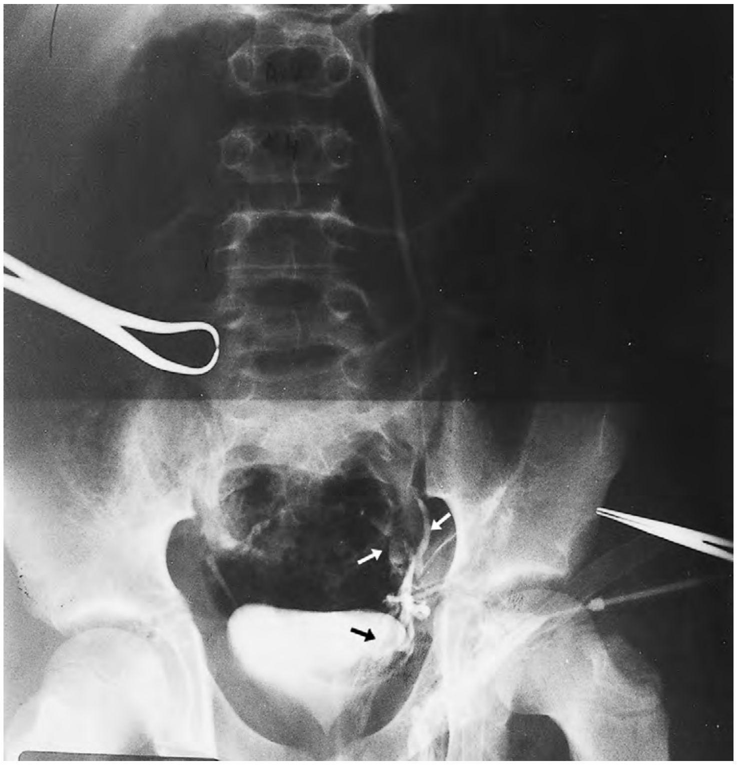

Figure 45-5 Retroperitoneal collateral venous filling of the internal spermatic vein *(arrows)* after previous inguinal varicocelectomy demonstrated by intraoperative internal spermatic postligation venography (ISPLV).

similarly demonstrated a 1.3% recurrence with artery ligation.[46] Another study noted identical improvements in semen quality in patients undergoing mass ligation including the artery and in those undergoing artery preservation[47]; testicular volumes were also similar in both groups, and pregnancy rates were not significantly different.

Despite these findings, passionate arguments have been made against routine arterial ligation, indicating that lack of atrophy afterward may well be a crude end point and that seminiferous tubule dysfunction may result.[48] Because biopsies are not routinely done after varicocelectomy and because semen analysis reflects the contributions of both testes, we have no extensive experience validating this concern. However, related experimental animal data supporting the concern of seminiferous tubular damage after arterial ligation do exist. Furthermore, testicular artery ligation makes the possibility of vasectomy later in life more risky, because the significant remaining testicular blood supply is derived from the vasal vessels. Later inguinal hernia repair also potentially puts the testicle at increased risk for atrophy. In patients with prior inguinal surgery, arterial ligation during varicocelectomy in adolescence may endanger the testis because arterial collaterals may have been previously divided. One report described no instances of atrophy among 13 boys with prior inguinal surgeries who were followed-up 1 year after laparoscopic ligation of both the testicular arteries and veins.[49]

Role of Venography

In an effort to minimize the risk of varicocele persistence or recurrence after open surgical varicocelectomy, the technique of intraoperative internal spermatic postligation venography (ISPLV) was developed.[8] Internal spermatic vein venography had previously been used preoperatively or intraoperatively to define venous anatomy, but its intraoperative use *after* the varicocele was ligated represented a new application.

After the varicocelectomy is completed, a single vein is cannulated with a large-bore angiocatheter or a 5F (1.69-mm) or 8F (2.64-mm) pediatric feeding tube placed retrograde toward the testis, which is secured in place with a silk suture (Fig. 45-6). A 30% intravenous contrast solution (1 mL contrast agent per kilogram of body weight) is rapidly injected, and C-arm angiographic films are exposed. The system is then flushed with intravenous 0.9% normal saline solution.

Performance of the venogram in this fashion after varicocelectomy is completed demonstrates residual "bypass" collaterals predisposing to varicocele recurrence that may not be visually recognized (see Fig. 45-5). Personal experience with this technique in two separate studies with children indicated that collaterals exist and fill the internal spermatic system with surprising frequency, despite the impression that the varicocelectomy was complete. Proximal bypass collaterals were noted in one third and pelvic venous collaterals were noted in about one half of the patients.[8,50] These latter pelvic collaterals filled, in diminishing order of frequency, the ipsilateral external iliac vein, hypogastric vein, external pudendal vein, deferential veins, suprapubic and retropubic crossover veins, the contralateral external and internal iliac veins, and the contralateral lumbosacral crossover veins. These veins were found to be unimportant clinically, because follow-up in virtually all instances did not demonstrate varicocele recurrence despite their presence and preservation. Varicocelectomy performed by the inguinal route was associated with a higher frequency of proximal collaterals than was varicocelectomy by the suprainguinal retroperitoneal route.

Occult veins existing within the testicular periarterial sheath, which subsequently hypertrophied after varicocele ligation, were the usual source for persisting collateralization. ISPLV led to eventual identification and division of these and other proximal collaterals, with repeat ISPLV then demonstrating lack of proximal filling. Use of this technique reduced the overall recurrence rate to between 3.5% and 6% and also demonstrated that most postoperative failures result from persistence of unrecognized proximal communicating veins due to incomplete initial ligations rather than from later recanalizations.[50]

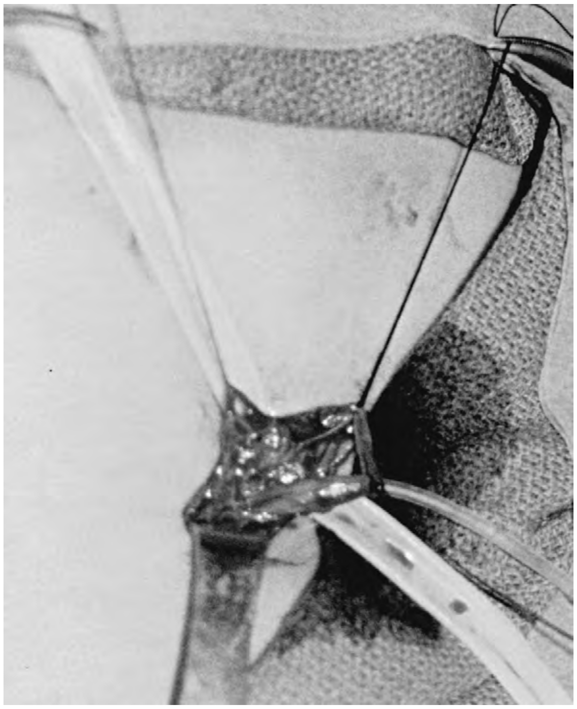

Figure 45-6 Intraoperative internal spermatic postligation venography (ISPLV) during suprainguinal open retroperitoneal varicocelectomy. An 8F (2.64-mm) feeding tube is secured distally toward the testis for injection of contrast materials.

Arguments for or against adjunctive use of ISPLV exist. Clearly, little benefit is added when mass ligation of the vessels is performed. The superior results obtained with the added magnification provided by microsurgical and laparoscopic varicocelectomy without use of ISPLV suggest that identification, dissection, and division of the periarterial venules with arterial preservation, which can safely be done in most cases, is the paramount factor. However, when open surgery is performed, even with the assistance of optical loupe magnification, ISPLV is beneficial.

Frequency of Bilaterality

Controversy exists regarding the frequency of unrecognized bilateral varicoceles and their potential significance. A growing body of evidence suggests that many (if not most) varicoceles are bilateral, with the right varicocele often undetected by physical examination. Twenty-eight adolescent boys with suspected or confirmed varicoceles were evaluated by scrotal thermography and bilateral spermatic vein venography; in 87.5%, the varicocele on the right side was not detected by physical examination alone but only by thermography and subsequent venographic confirmation.[51] This study was important in that venographic confirmation was used to confirm the finding. Other studies have demonstrated the high prevalence of bilateral varicoceles in infertile men (77%)[52] and the fact

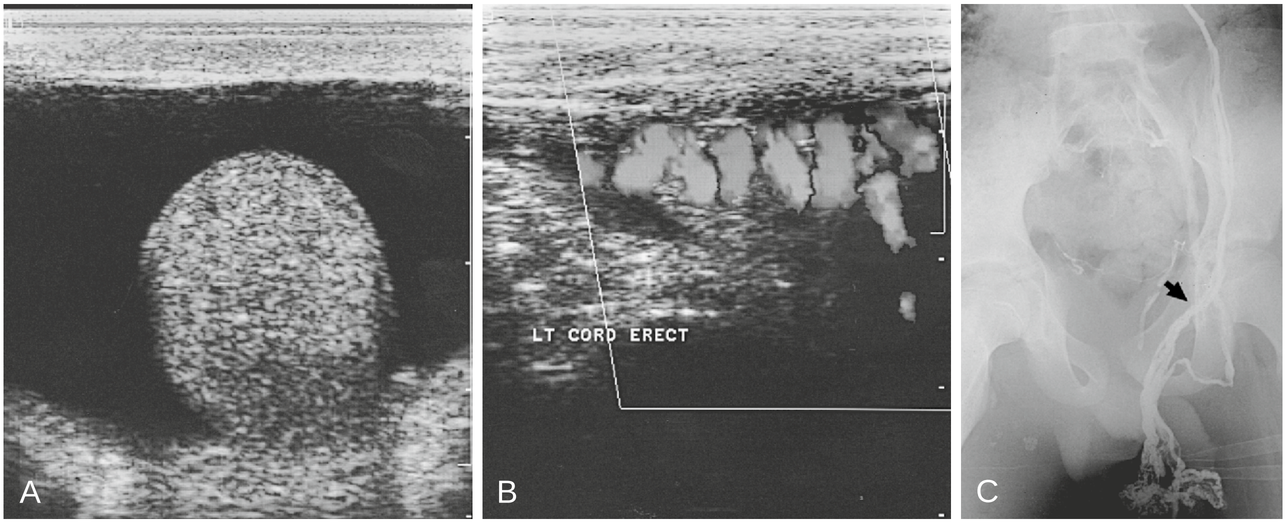

Figure 45-7 Duplex sonographic demonstration of an enlarging hydrocele and persisting varicocele in a 12-year-old boy 2 years after left inguinal varicocelectomy. **A,** Large scrotal hydrocele. **B,** Retrograde enlargement of varicosities demonstrated on sonography with the Valsalva maneuver with the patient in the upright position. **C,** Intraoperative scrotal venogram demonstrates persistent filling of the internal spermatic vein at and above the level of the internal inguinal ring *(arrow).* Scrotal hydrocelectomy and open high suprainguinal retroperitoneal varicocelectomy resolved each problem.

that bilateral varicocelectomy leads to significantly greater improvement in postoperative semen parameters in men with repaired large left varicoceles and grade 1 right varicoceles, compared to unilateral left varicocelectomy alone.[53] Although pediatric varicocele repair usually focuses only on short-term outcomes, these findings indicate that a strong suspicion should be maintained in these patients regarding diagnosis of occult right-sided varicocele and the long-term fertility implications.

Treatment of Recurrences

Persistent or recurrent varicocele after seemingly adequate varicocelectomy represents a very difficult treatment problem. Anxiety and stress levels are high for the patient, the parents, and the treating surgeon. Reoperation is indicated, because the original goals of surgery are not fulfilled, and the original risks associated with nonoperative treatment remain.

Most persisting varicoceles in adolescents are identified within several months after the original surgery. Delayed recanalizations are less common.[3] Clinical diagnosis is made in the same manner as was done initially—that is, by physical examination and complementary ultrasonography, if needed. If recurrence is confirmed, a carefully planned reexploration is indicated. Use of intraoperative venography at the onset of the reexploration in these circumstances is helpful to demonstrate the pathologic venous anatomy (Fig. 45-7).

With the patient in a reverse Trendelenburg position causing filling of the scrotal varicose veins, a small scrotal incision is made, and a dilated vein is isolated between silk ties. The vein is cannulated with a large-bore angiocatheter or a 5F or 8F pediatric feeding tube, which is placed retrograde directed away from the testis and secured in place with a silk suture. Rapid injection of a 30% intravenous contrast solution (1 mL contrast agent per kilogram of body weight) is made, followed by C-arm angiographic x-ray exposures. This procedure usually demonstrates proximal bypass collateral veins at or near the site of the original ligation, although in rare instances, other contributory sites are identified. Three of 15 patients investigated by this technique were shown to have persisting varicoceles with completely ligated internal spermatic veins. The catheter is removed, and the vein is ligated; the small scrotal incision is closed with absorbable sutures. If the original procedure was performed transinguinally, a suprainguinal open or laparoscopic reexploration is done. If it was initially done retroperitoneally, a laparoscopic higher reexploration is appropriate. Early data indicate that microsurgical repair is effective for recurrences resulting from initial varicocelectomy performed by either route.[54]

RESULTS OF TREATMENT

Comparison of the various approaches to treatment of adolescent varicoceles is difficult, because published results diverge widely. Initial evaluation outcomes consist of varicocele cure, absence of hydrocele, observation of satisfactory testicular catch-up growth, and, if available, assessment of hormonal and semen parameters. One series contrasting four different methods of treatment (high mass ligation of vessels, high ligation with artery sparing, artery-sparing inguinal, and laparoscopic) indicated a clear advantage for the open high retroperitoneal approach with artery preservation, including the least risk of hydrocele or persisting varicocele.[55] Other series had divergent results, with varied frequencies of hydrocele occurrence and varicocele persistence, although catch-up growth was described in most. Sperm concentration appears to improve in patients treated successfully by any approach.

The late important outcome parameter of significance, paternity, cannot yet be significantly evaluated, because most boys treated in adolescence are just becoming of age. One study demonstrated a 100% paternity rate in a cohort of 18 men who had undergone adolescent varicocelectomy.[56]

VARICOCELECTOMY IN ADOLESCENTS WITH PREVIOUS TESTICULAR CONDITIONS POTENTIALLY AFFECTING FERTILITY

Boys with previous testicular pathology are at increased risk for infertility when a varicocele appears. Examples of such previous pathology include right or left cryptorchidism,

Table 45-5 **Results of Semen Analysis Before and After Left Varicocelectomy**

Time	Volume (mL)	Sperm Concentration (/mL)	Motility (%)	Morphology (%)	pH	Fructose
Preoperative	1.3	0	0	0	8.2	+
6 mo	2.2	$>2 \times 10^6$	>50	>30	8.6	+
6 mo	2.6	1×10^6	43	22	8.1	+
12 mo	1.5	0.4×10^6	40	30	8.5	+

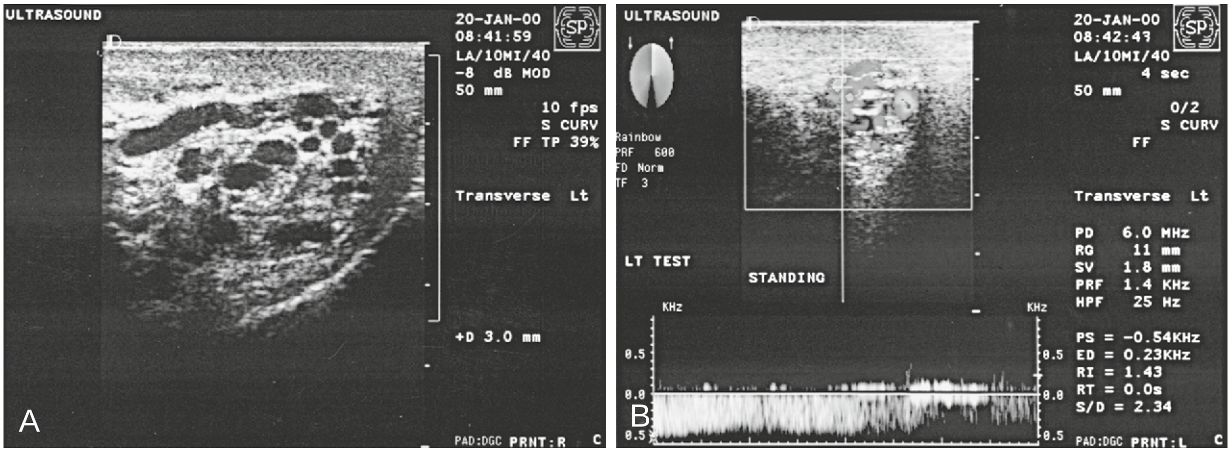
ULTRASOUND
20-JAN-00
08:41:59
LA/10MI/40
-8 dB MOD
50 mm
10 fps
S CURV
FF TP 39%
Transverse Lt
+D 3.0 mm
PAD:DGC PRNT:R
C
A
ULTRASOUND
20-JAN-00
08:42:43
LA/10MI/40
4 sec
50 mm
0/2
S CURV
FF
Rainbow
PRF 600
FD Norm
TF 3
Transverse Lt
LT TEST
STANDING
PD 6.0 MHz
RG 11 mm
SV 1.8 mm
PRF 1.4 KHz
HPF 25 Hz
KHz
KHz
0.5
0.0
0.5
PS = -0.54KHz
ED = 0.23KHz
RI = 1.43
RT = 0.0s
S/D = 2.34
PAD:DGC PRNT:L
C
B

Figure 45-8 Duplex sonogram in a 15-year-old pubertal boy with absent right testicle from perinatal torsion and left varicocele. The solitary left testicle is markedly hypertrophied, measuring 50 mL in volume. **A,** Large varicosities are noted in the spermatic cord. **B,** Retrograde venous filling is noted during the Valsalva maneuver.

congenitally absent right testis, acquired right testis absence (from tumor, trauma, or torsion), and right or left testis atrophy (from infection or other contributory causes). If unilateral cryptorchidism was present, studies indicate that impaired germ cell production may be bilateral even though one testis was descended.[57] In all these circumstances, the additional infertility risk resulting from the varicocele effect may be additive, and aggressive treatment of the varicocele should be pursued (Table 45-5 and Fig. 45-8).

In one series in which left varicocelectomy was performed in 15 subfertile men with absent or atrophic right testes, sperm concentrations rose significantly in 14, strongly indicating the deleterious effect of the varicocele on testicular function in this clinical setting.[58] The diagnostic approach and treatment need to be individualized in these patients, and additional diagnostic studies are often indicated besides simple clinical examination, including testicular ultrasonography to determine testis size; serum FSH, LH, and testosterone measurements; semen analysis; and testicular biopsy.[19]

CONCLUSIONS

Significant evolution in the treatment of adolescent varicoceles has occurred since 1970. These varicoceles are now recognized as being the source of those varicoceles seen in men presenting later with small testes and infertility. Varicocelectomy in adolescence is a highly successful undertaking, resulting in resolution of the varicocele and catch-up growth of the testis in most instances. As the surgical approaches are further refined, additional improved results of treatment are expected, minimizing the frequency of postoperative hydrocele and varicocele persistence. Recognition of the contributory role of the adolescent varicocele to male infertility and the importance of treating adolescent varicoceles should significantly reduce the number of subfertile adults in the future.

REFERENCES

For complete list of references log onto www.expertconsult.com

PART VII

NEPHROUROLOGY

CHAPTER 46

ACUTE KIDNEY INJURY AND CHRONIC KIDNEY DISEASE IN CHILDREN

Sharon Phillips Andreoli

Acute kidney injury (AKI) (previously called acute renal failure, or ARF) is characterized by a reversible increase in the blood concentration of creatinine and nitrogenous waste products and by the inability of the kidney to appropriately regulate fluid and electrolyte homeostasis. Chronic kidney disease (CKD) (previously called chronic renal failure, or CRF) results in similar alterations in fluid and electrolyte balance, but the metabolic derangements are irreversible. There are many causes of AKI and CKD, and the more common ones are listed in Table 46-1. Some diseases, such as the tumor lysis syndrome, drug-induced interstitial nephritis, aminoglycoside nephrotoxicity, and other toxic nephropathies, usually manifest as AKI, and recovery is usually complete. Others, such as rapidly progressive glomerulonephritis (RPGN), may manifest as AKI but rapidly evolve into CKD. Several renal diseases, such as the hemolytic-uremic syndrome (HUS), Henoch-Schönlein purpura, and obstructive uropathy with associated renal dysplasia, may manifest as AKI with improvement of renal function to normal or near-normal levels, but afterward the child's renal function may slowly deteriorate, leading to CKD several months to years later. In contrast, renal dysplasia with or without associated obstructive uropathy and renal disease such as juvenile nephronophthisis typically slowly evolve into CKD over a period of several years.

Because of the more rapid development of the metabolic derangement characteristic of AKI, children with AKI typically present with symptoms of uremia, acidosis, anemia, and fluid overload, whereas children with undiagnosed CKD may have relatively few symptoms until uremia is advanced. Children with AKI due to hypoxic/ischemic insults, HUS, acute nephritis, and certain other causes are more likely to demonstrate oliguria or anuria (urine output <400 to 500 mL/24 hr in older children or <0.5 to 1.0 mL/kg/hr in younger children and infants). Children with acute interstitial nephritis (AIN), nephrotoxic renal insults including aminoglycoside nephrotoxicity, or contrast nephropathy are more likely to have AKI with normal urine output. Several studies have shown that the morbidity and mortality of nonoliguric AKI are substantially less than that of oliguric renal failure.[1-5] Because CKD may evolve over a long period, symptoms of uremia, anemia, and acidosis are slowly progressive and may not be apparent until renal failure is advanced. Similarly, because the kidney can slowly adapt to nephron loss, urine output remains adequate and serum electrolytes concentrations (e.g., potassium) remain normal despite severe CKD. Anemia, growth failure, and renal osteodystrophy are also important complications of CKD. This chapter reviews the common causes of AKI and CKD and the management of renal failure including renal replacement therapy.

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

Although the precise incidence and prevalence of AKI in pediatric patients are unknown, studies suggest that the incidence of AKI among hospitalized children is increasing.[6-13] In a large study of adult patients, the incidence of AKI was 209 per 1 million population, and the most common cause of AKI was prerenal failure in 21% of patients and acute tubular necrosis (ATN) in 45% of patients.[8] Similar epidemiologic studies have not been performed in pediatric patients, but hypoxia/ischemia and nephrotoxins have been shown to be important causes of AKI in neonates, children, and adolescents.[3-12] In a study of pediatric patients in a tertiary care center, 227 children received dialysis therapy during an 8-year period for an overall incidence of 0.8 cases per 100,000 total population.[4] In a study of neonates, the incidence of AKI ranged from 8% to 24% of newborns, and AKI was particularly common among neonates who had undergone cardiac surgery.[3-13] Asphyxiated neonates had a high incidence of AKI, whereas AKI was less common among neonates with moderate asphyxia. The AKI was nonoliguric, oliguric, and anuric in 60%, 25%, and 15% of the cases, respectively.[3-13]

Very low birth weight (<1500 g), low Apgar score, patent ductus arteriosus, and maternal administration of antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with the development of AKI.[9] Moreover, low Apgar score and maternal ingestion of NSAIDs have been associated with decreased renal function in preterm infants.[10,14] The incidence of AKI among newborns in a developing county was 3.9 per 1000 live births, with 34.5 of 1000 newborns admitted to the neonatal care unit.[11]

In addition to environmental factors, some newborns may have genetic risk factors for AKI. Polymorphism of the angiotensin-converting enzyme (ACE) gene or of the angiotensin receptor gene, with resultant alterations in activity of the renin-angiotensin system, might play a role in the development of AKI.[15] In studies in newborns, polymorphisms of the genes encoding tumor necrosis factor-α (TNF-α), interleukin-1b (IL1B), IL6, and IL10 were investigated to determine whether they would lead to a more intense inflammatory response and predispose newborns to AKI.[16] The allelic frequency of the individual genes did not differ between newborns with

Table 46-1 Common Causes of Acute Kidney Injury and Chronic Kidney Disease

- **Prerenal Failure**
- Decreased true intravascular volume
- Decreased effective intravascular volume
- **Intrinsic Renal Disease**
- Acute tubular necrosis (vasomotor nephropathy)
    - Hypoxic/ischemic insults
    - Drug-induced
    - Toxin-mediated
        - Endogenous toxins—hemoglobin, myoglobin
        - Exogenous toxins—ethylene glycol, methanol
- Uric acid nephropathy and tumor lysis syndrome
- Interstitial nephritis
    - Drug-induced
    - Idiopathic
- Glomerulonephritis
- Vascular lesions
    - Renal artery thrombosis
    - Renal vein thrombosis
    - Cortical necrosis
    - Hemolytic-uremic syndrome
- Hypoplasia/dysplasia with or without obstructive uropathy
    - Idiopathic
    - Exposure to nephrotoxic drugs in utero
- Hereditary renal disease
    - Autosomal dominant polycystic kidney disease
    - Autosomal recessive polycystic kidney disease
    - Alport syndrome
    - Sickle cell nephropathy
    - Juvenile nephronophthisis
- **Obstructive Uropathy**
- Obstruction in a solitary kidney
- Bilateral ureteral obstruction
- Urethral obstruction

AKI and those without AKI, but the TNF-α/IL6 AG/GC haplotype was present in 26% of newborns who developed AKI compared to 6% of newborns who did not develop AKI. The investigators suggested that the combination of these polymorphisms might lead to a greater inflammatory response and the development of AKI in neonates with infection.[16] As described later, future therapies for AKI might involve strategies to interrupt the inflammatory response.

In other studies, the incidence of ACE I/D allele genotypes or variants of the angiotensin I receptor gene did not differ in neonates with AKI compared to neonates without AKI, but they may be associated with patent ductus arteriosus and heart failure and indirectly contribute to CKD.[15,17] AKI occurred more commonly in very-low-birth-weight neonates carrying the heat shock protein 72 (1267)GG genetic variation, which is associated with low inducibility of heat shock protein 72.[18] Given the important role of heat shock proteins in ischemic renal injury, this finding suggests that some neonates are more susceptible to ischemic injury.[19] Future studies of the genetic background of the child at risk for AKI due to medication exposure, toxin exposure, ischemic hypoxic insults, or other insults are likely to affect management in the child who has or is at risk for AKI.

ETIOLOGY OF ACUTE KIDNEY INJURY AND CHRONIC KIDNEY DISEASE

Table 46-1 provides a partial listing of the many diverse causes of AKI and CKD in children. Renal failure can be divided into prerenal failure, intrinsic renal disease including vascular insults, and obstructive uropathies. Some causes of AKI, such as cortical necrosis or renal vein thrombosis, occur more commonly in neonates, whereas HUS is more common in young children, and RPGN typically occurs in older children and adolescents. CKD from dysplastic kidneys can manifest in the neonatal period with pulmonary hypoplasia, joint contractures, low-set ears, and other stigmata of Potter syndrome. In other cases, CKD manifests in childhood or adolescence with symptoms of anemia, growth failure, and renal osteodystrophy. An important cause of AKI and CKD in neonates is exposure to material drugs in utero that interfere with nephrogenesis, such as ACE inhibitors, angiotensin receptor blockers, and NSAIDs.[20-24] The history, physical examination, and laboratory studies, including a urinalysis and radiographic studies, can establish the likely cause of AKI or CKD. In some instances, such as AKI occurring in hospitalized children, multiple factors are likely to be implicated.

Prerenal Failure

Prerenal failure occurs when blood flow to the kidney is reduced as a result of true intravascular volume contraction or a decreased effective blood volume, as described later. Because the kidneys are intrinsically normal, prerenal failure is reversible once the blood volume and hemodynamic conditions are restored to normal. Prolonged prerenal failure can result in intrinsic AKI due to hypoxic/ischemic ATN. The evolution of prerenal failure to intrinsic renal failure is not sudden, and several compensatory mechanisms maintain renal perfusion when renal hemodynamics is not optimal.

When renal perfusion is compromised, the afferent arteriole relaxes its vascular tone to decrease renal vascular resistance and maintain renal blood flow. During renal hypoperfusion, the intrarenal generation of vasodilatory prostaglandins including prostacyclin mediates vasodilation of the renal microvasculature to maintain renal perfusion.[25,26] Administration of cyclooxygenase inhibitors such as aspirin or NSAIDs can inhibit this compensatory mechanism and precipitate acute renal insufficiency.[26,27] Similarly, when renal perfusion pressure is low, as in renal artery stenosis, the intraglomerular pressure necessary to drive filtration is in part mediated by increased intrarenal generation of angiotensin II to increase efferent arteriolar resistance.[28-30] Administration of ACE inhibitors in these conditions can eliminate the pressure gradient needed to drive filtration and precipitate AKI.[28-30] Therefore, administration of medications that can interfere with compensatory mechanisms to maintain renal perfusion may precipitate AKI in certain clinical circumstances.

Prerenal failure caused by true volume contraction can result from hemorrhage, dehydration due to gastrointestinal losses, salt-wasting renal or adrenal diseases, central or nephrogenic diabetes insipidus, increased insensible losses such as occurs in burns, and disease states associated with third-space losses, such as sepsis, nephrotic syndrome, traumatized tissue, and capillary leak syndrome. Decreased effective blood volume occurs when the true blood volume is normal or increased but renal perfusion is decreased due to diseases such as congestive heart failure, cardiac tamponade, and hepatorenal syndrome.[1-5,29,30] Whether prerenal failure is caused by true volume depletion or decreased effective blood volume, correction of the underlying disturbance will return renal function to normal.

Several measures of urinary parameters, including urine osmolality, urine sodium concentration, fractional excretion of sodium, and the renal failure index, have been proposed to help differentiate prerenal failure from vasomotor nephropathy (ATN). In prerenal failure, the renal tubules are working appropriately and are able to conserve salt and water appropriately, whereas in vasomotor nephropathy the tubules have progressed to irreversible injury and are unable to conserve salt appropriately.[1-5,31-33] During prerenal failure, the tubules are able to respond to decreased renal perfusion by appropriately conserving sodium and water so that the urine osmolality remains greater than 400 to 500 mOsm/L, urine sodium is less than 10 to 20 mEq/L, and the fractional excretion of sodium is less than 1%.

Because the renal tubules in newborns and premature infants are relatively immature compared with those in older infants and children, the corresponding values suggesting renal hypoperfusion are urine osmolality greater than 350 mOsm/L, urine sodium less than 20 to 30 mEq/L, and a fractional excretion of sodium of less than 2.5%.[32,33] If the renal tubules have sustained injury, as occurs in ATN, they cannot conserve sodium and water appropriately, so the urine osmolality becomes less than 350 mOsm/L, the urine sodium greater than 30 to 40 mEq/L, and the fractional excretion of sodium greater than 2.0%. However, the use of these numbers to differentiate prerenal failure from ATN requires that the patient have normal tubular function initially. Although this may be the case in some children, newborns with immature tubules and children with preexisting renal disease, salt-wasting renal adrenal disease, or other conditions may have prerenal failure with urinary indices suggestive of ATN. Therefore, it is essential to consider the function of the tubules before the potential insult that might have precipitated vasomotor nephropathy/ATN.

Intrinsic Renal Disease

Acute Tubular Necrosis

Hypoxic/Ischemic Acute Tubular Necrosis

Hypoxic/ischemic ATN is also called *vasomotor nephropathy,* because the renal failure is characterized by early vasoconstriction followed by patchy cortical necrosis. The pathogenesis of ATN is complex and is related to alterations in intrarenal hemodynamics, the generation of reactive oxygen molecules and free radicals, depletion of adenosine triphosphate (ATP), and loss of normal cell polarity.[34-39] Leukocyte endothelial cell adhesion molecules have been shown to be upregulated in ATN, and the administration of anti–adhesion molecule antibodies can substantially decrease renal injury in animal models of ATN.[37] Although there is no current specific therapy to prevent renal injury or promote recovery in human ATN, several potential therapies are being studied, and future management of AKI may also include antioxidant and anti–adhesion molecule therapy or the administration of growth factors to promote recovery.[38,39]

In hypoxic/ischemic ATN, the urinalysis may be unremarkable or may demonstrate low-grade proteinuria and granular casts; urine indices of tubular function demonstrate an inability to conserve sodium and water, as described previously. The creatinine concentration typically increases by about 0.5 to 1.0 mg/dL per day. Radiographic studies demonstrate kidneys of normal size with loss of corticomedullary differentiation, whereas a radionuclide renal scan with technetium 99m–labeled mercaptoacetyltriglycerine (Tc^{99m}-MAG3) or diethylenetriamine penta-acetic acid (Tc^{99m}-DTPA) demonstrates normal or slightly decreased renal blood flow with poor function, delayed accumulation of the radioisotope in the renal parenchyma, and no excretion of the isotope in the collecting system (Fig. 46-1A).

Except in very severe insults in which microthrombi formation leads to the development of cortical necrosis, the prognosis of ATN is good and depends on the underlying events that precipitated the ischemic/hypoxic insult. Mortality and morbidity from AKI are much worse in children and neonates with multiorgan failure; the child does not die of renal failure but rather with renal failure and the associated conditions.[1-5,40] In children who recover from ATN, the renal function returns to normal but the time to recovery is quite variable. Some children begin to recover renal function within days after the onset of renal failure, whereas recovery may not occur for several weeks in other children. Recovery of renal function may be accompanied by a diuretic phase with voluminous urine output at a time when the tubules are beginning to recover but have not recovered sufficiently to reabsorb solute and water appropriately. If such a diuretic phase occurs, close attention to fluid and electrolyte balance is essential.

Nephrotoxic Renal Failure

Medications associated with renal failure resulting, at least in part, from toxic tubular injury include aminoglycoside antibiotics, intravascular contrast media, amphotericin B, chemotherapeutic agents such as ifosfamide and cisplatin, acyclovir, and acetaminophen; other medications have been implicated less commonly.[41,42]

Aminoglycoside nephrotoxicity typically manifests with nonoliguric AKI and a urinalysis showing minimal urinary abnormalities.[42] The incidence of aminoglycoside antibiotic nephrotoxicity is related to the dose and duration of the antibiotic therapy as well as the level of renal function before its initiation. The cause is thought to be related to the lysosomal dysfunction of proximal tubules and is reversible once the aminoglycoside antibiotics have been discontinued. However, the serum creatinine may continue to increase for several days due to ongoing tubular injury from continued high parenchymal levels of the aminoglycoside.

Patients with preexisting renal disease, diabetes, or dehydration are at higher risk for the development of nephrotoxic renal dysfunction from the administration of intravascular contrast media.[43] The incidence of contrast nephropathy can be reduced with the use of nonionic, low-osmolality contrast media. NSAIDs may precipitate AKI by their effect on intrarenal hemodynamics.[25,26] Cisplatin, ifosfamide, acyclovir, amphotericin B, and acetaminophen are also nephrotoxic and may precipitate AKI.[41,44-46] Several other drugs have also been associated with AKI, but the incidence is less common.

Hemolysis and rhabdomyolysis from any cause can result in sufficient hemoglobinuria or myoglobinuria to induce tubular injury and precipitate AKI. The mechanisms of injury are complex but may be related to vasoconstriction, precipitation of the pigments in the tubular lumen, or heme protein–induced oxidant stress, or a combination of these.[47] If the rhabdomyolysis is a result of tissue injury

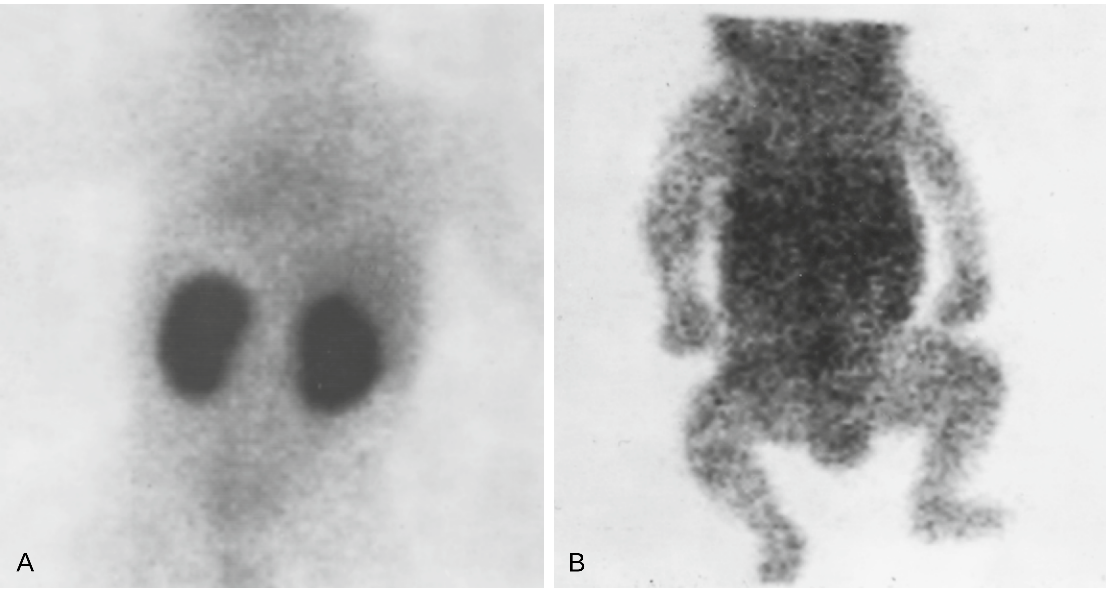

Figure 46-1 Tc^{99m}-MAG3 renal scan in a 1-year-old with acute tubular necrosis (ATN) **(A)** and in a newborn with cortical necrosis **(B).** Each scan was taken 4 hours after injection of the isotope. **A,** In the child with ATN, there is delayed uptake of isotope with parenchymal accumulation of isotope and little to no excretion of isotope into the collecting system. **B,** In contrast, no renal parenchymal uptake of isotope is demonstrated in a neonate with cortical necrosis. (**A** and **B,** From Andreoli SP. Clinical aspects and management of acute renal failure in children. In: Barratt TM, Avner ED, Harmon WE, eds. *Pediatric Nephrology.* Baltimore: Williams & Wilkins; 1998:1119-1124.)

with substantial third-space fluid losses, as occurs in a crush injury, rapid fluid resuscitation can prevent or limit the renal injury.[47]

Uric Acid Nephropathy and Tumor Lysis Syndrome

Children with acute lymphocytic leukemia or B-cell lymphoma have the highest risk of AKI due to uric acid nephropathy or the tumor lysis syndrome or both.[48,49] Although the pathogenesis of uric acid nephropathy is complex, a potentially important mechanism of injury involves the precipitation of uric acid crystals in the tubules to obstruct urine flow or in the renal microvasculature to obstruct renal blood flow.[48-50]

A common cause of AKI in leukemia is the development of the tumor lysis syndrome during chemotherapy.[49-50] Therapy with allopurinol limits the increased excretion of uric acid during chemotherapy but results in a markedly increased excretion of uric acid precursors, including hypoxanthine and xanthine.[48] Xanthine is less soluble than uric acid, and precipitation of hypoxanthine and xanthine may play a role in the development of AKI during the tumor lysis syndrome. The tumor lysis syndrome results in rapid increases in serum levels of potassium, blood urea nitrogen (BUN), purine metabolite products, and phosphorus, with a reciprocal decrease in the serum calcium level as tumor cells are lysed.

Renal failure due to tumor lysis syndrome is transient, and the patient eventually recovers renal function once tumor lysis is complete. However, frequent hemodialysis or continuous hemofiltration may be necessary to control hyperkalemia and other metabolic abnormalities resulting from the rapid lysis of tumor cells.[48-50]

Acute Interstitial Nephritis

AIN can cause renal failure as a reaction to a drug, or it can be idiopathic. Children with AIN may have rash, fever, arthralgias, eosinophilia, and pyuria with or without eosinophiluria. Radiographic studies demonstrate large echogenic kidneys, and a kidney biopsy demonstrates interstitial infiltrate with many eosinophils. Medications commonly associated with AIN include methicillin and other penicillin analogues, cimetidine, sulfonamides, rifampin, and NSAIDs; other drugs have been associated less commonly.[51] AIN caused by NSAIDs may also manifest with high-grade proteinuria and nephrotic syndrome.

Specific therapy for AIN includes withdrawal of the implicated drug. In addition, corticosteroids may aid in the resolution of the renal failure.

Rapidly Progressive Glomerulonephritis

Any form of glomerulonephritis in its most severe degree can manifest with AKI and RPGN. The clinical features include hypertension, edema, hematuria that is frequently gross, and rapidly rising concentrations of BUN and creatinine. The characteristic pathologic finding in RPGN is extensive crescent formation. Glomerulonephritis as a cause of AKI and CKD is discussed in another chapter. RPGN due to postinfectious glomerulonephritis does not lead to CKD, whereas other glomerulonephritides, such as antineutrophil cytoplasmic antibody (ANCA)-positive glomerulonephritis, Goodpasture syndrome, and idiopathic RPGN, typically manifest with AKI and may quickly evolve into CKD with or without therapy.[52] Serologic tests including antinuclear antibody (ANA), ANCA, and anti–glomerular basement membrane (anti-GBM) titers and complement studies are required to evaluate the cause of the RPGN. Because specific therapy depends on the pathologic findings, a biopsy should be performed relatively promptly when a child presents with clinical characteristics suggestive of RPGN.

Vascular Insults

Large-vessel insults such as renal artery thrombosis and renal vein thrombosis produce AKI only if they are bilateral or if occur in a solitary kidney. Microvascular insults occur in cortical necrosis, in typical (diarrhea-positive) and atypical (diarrhea-negative) HUS, and in HUS after bone marrow transplantation.

RENAL ARTERY THROMBOSIS AND RENAL VENOUS THROMBOSIS

Renal artery thrombosis and renal venous thrombosis occur much more commonly in newborns and small children than in older children. Renal artery thrombosis is strongly associated with an umbilical artery line and a patent ductus arteriosus.[53] In addition to AKI, children may demonstrate hypertension, gross or microscopic hematuria, thrombocytopenia, and oliguria. In renal artery thrombosis, the initial ultrasound scan may appear normal or may demonstrate minor abnormalities, whereas a renal scan demonstrates little to no blood flow. In renal vein thrombosis, ultrasound demonstrates an enlarged, swollen kidney, whereas the renal scan typically demonstrates decreased blood flow and function.

Therapy should be aimed at limiting extension of the clot by removal of the umbilical arterial catheter; anticoagulant therapy may be considered, particularly if the clot is large.[53-55]

CORTICAL NECROSIS

Cortical necrosis as a cause of AKI is much more common in younger children, particularly in neonates. Cortical necrosis is associated with hypoxic/ischemic insults resulting from perinatal anoxia, placenta abruption, and twin-twin or twin-maternal transfusions with resultant activation of the coagulation cascade. Children and newborns with cortical necrosis usually have gross or microscopic hematuria and oliguria and may have hypertension as well.[56] In addition to laboratory features of elevated BUN and creatinine concentrations, thrombocytopenia may be present as a result of the microvascular injury. Radiographic features include a normal renal ultrasound study in the early phase; in later phases, ultrasonography may show that the kidney has undergone atrophy and substantially decreased in size. A radionucleotide renal scan shows decreased to no perfusion with delayed or no function (see Fig. 46-1B), in contrast to the delayed function that is observed in ATN (see Fig. 46-1A).

The prognosis for cortical necrosis is much worse than that for ATN. Children with cortical necrosis may have partial recovery or no recovery at all. Typically, children with cortical necrosis need short-term or long-term dialysis therapy, but those who do recover sufficient renal function are at risk for the late development of CKD.

HEMOLYTIC-UREMIC SYNDROME

HUS is a common cause of AKI in children and leads to substantial morbidity and mortality as well as long-term complications that may not become apparent until adulthood.[57,58] Typical HUS usually follows a gastrointestinal illness characterized by hemorrhagic colitis associated with infection by Shiga-like toxin–producing *Escherichia coli*, of which O157:H7 is the most common serotype. Approximately 10% of children with hemorrhagic colitis associated with Shiga-like toxin–producing *E. coli* develop HUS.[58,59] At the time the diarrhea is subsiding, the child appears pale and lethargic due to the hemolytic anemia. Oliguria and anuria occur in about 30% to 50% of affected children, and about 40% to 75% will need dialysis therapy.

HUS is a systemic disease in which the kidney and gastrointestinal tract are the organs most commonly affected; however, evidence of central nervous system, pancreatic, skeletal, and myocardial involvement may also be present.[59-63] Gastrointestinal involvement may lead to rectal prolapse, ischemic colitis, and transmural colonic necrosis. Pancreatic involvement manifested as elevated pancreatic enzymes occurs in 10% to 20% of affected children, and glucose intolerance due to pancreatic islet cell involvement occurs in fewer than 10%.[63] Central nervous system disease may manifest as seizures, coma, lethargy, and irritability.

Laboratory studies usually demonstrate the characteristic triad of HUS: microangiopathic hemolytic anemia, thrombocytopenia, and renal disease. Renal disease is manifested as hematuria or proteinuria or both, with elevated BUN and creatinine in most patients. However, epidemiologic studies performed during epidemics of HUS clearly show that some children have incomplete forms of HUS without the classic triad.[64] A high polymorphonuclear leukocyte (PMN) count with a prominent left shift is typical of the disease, and a high white blood cell (WBC) count is associated with more severe disease and a worse outcome.[65] Stool cultures usually yield Shiga-like toxin–producing *E. coli*, but the incidence of positive cultures decreases as the diarrhea subsides.[59] The yield of positive cultures is greatest in stool cultures obtained soon after the onset of the diarrhea.

During the acute phase of HUS, pathologic specimens of the kidney reveal microvascular injury characterized by microthrombi deposition in association with swollen and detached glomerular endothelial cells and infiltration of inflammatory cells.[66] Similar pathologic changes have been described in other organs, including the colon, central nervous system, pancreas, and skeletal and myocardial muscle.[67] The mechanisms of this microvascular injury are unknown, but evidence points to a role for Shiga-like toxins in mediating endothelial cell injury with a resultant change in the normal anticoagulant profile of the endothelial cell to a procoagulant state. Shiga-like toxins have direct effects on endothelial cells, and it is likely that inflammatory mediators are important in the pathogenesis of endothelial cell injury as well.[68-70] The PMN count is usually elevated and correlates with a poor outcome, and increased levels of IL8 and TNF-α have been described in children with HUS, suggesting that the inflammatory response, and PMNs in particular, are very important in mediating microvascular injury in HUS.[65-69]

Some studies have shown that administration of antibiotics to children with hemorrhagic colitis associated with Shiga-like toxin–producing *E. coli* significantly increased the odds of the child's developing HUS.[71] However, a meta-analysis did not demonstrate that antibiotic therapy was harmful.[72] Antibiotic therapy has the theoretical potential to alter the bacterial production of toxin, resulting in increased release of the toxin. Similarly, antimotility agents are also not indicated, because they may increase the systemic absorption of toxin as a result of the slower gastrointestinal transit time. Therapy for HUS is only supportive. In a multicenter, placebo-controlled clinical trial, the administration of a toxin-binding compound, 8-methoxycarbonyloctyl oligosaccharides (Synsorb-Pk), at the onset of HUS to diminish the severity of HUS and decrease the incidence of extrarenal complications was found to be ineffective.[73]

Renal Hypoplasia/Dysplasia

Renal dysplasia is frequently associated with obstructive uropathy including posterior urethral valves, ureteropelvic junction obstruction, prune-belly syndrome, megacystis-megaureter, and ureteroceles, which are each discussed in detail in other chapters. In the absence of obstruction, cystic renal dysplasia can be associated with a number of syndromes, including Meckel-Gruber syndrome and Zellweger syndrome.[74]

Renal hypoplasia/dysplasia may be isolated, or it may be associated with numerous syndromes including the Noonan, Denys-Drash, Turner, and Beckwith-Wiedemann.[74] Depending on the degree of hypoplasia/dysplasia, renal insufficiency can range from mild to severe. Regardless of the origin of the renal dysplasia, renal insufficiency is usually slowly progressive. An important cause of renal dysplasia is exposure to drugs in utero that interfere with nephrogenesis, such as ACE inhibitors, angiotensin receptor blockers, and NSAIDs.[20-24]

PROGNOSIS OF ACUTE KIDNEY INJURY

The prognosis of AKI is highly dependent on the underlying etiology.[3-7,12,13] Children who have AKI as a component of multisystem failure have a much higher mortality rate than those with intrinsic renal disease such as HUS, RPGN, and AIN. Recovery from intrinsic renal disease is also highly dependent on the underlying cause of the AKI. Children with aminoglycoside nephrotoxicity or ATN typically recover normal renal function; although in the past it was thought that such patients were at low risk for late complications, it has now been shown that CKD can evolve from AKI.[75-77] Children who have suffered substantial loss of nephrons, as from HUS or RPGN, are at risk for the late development of renal failure long after the initial insult. As several studies in animal models have documented, hyperfiltration of the remnant nephron may eventually lead to progressive glomerulosclerosis of the remaining nephrons.[78] Therefore, children who have had cortical necrosis during the neonatal period and recovered renal function and children with an episode of severe Henoch-Schönlein purpura or HUS are clearly at risk for the late development of renal complications. Such children need lifelong monitoring of their renal function, blood pressure, and urinalysis.

It was previously thought that AKI due to hypoxic/ischemic or nephrotoxic insults was reversible with return of renal function to normal, but more recent studies demonstrated that such insults can lead to physiologic and morphologic alterations in the kidney that may result in kidney disease at a later time.[77] Therefore, AKI from any cause can be a concern for later kidney disease. Importantly, AKI is likely to be especially deleterious if the kidney is not yet grown to adult size or the full complement of nephrons has not yet developed. Because nephrogenesis is not complete until approximately 34 weeks of gestation, AKI during this interval might lead to a decreased nephron number; studies have in fact suggested that AKI during nephrogenesis results in decreased nephron number and subsequent glomerulomegaly.[78,79] AKI in the full-term neonate is also associated with later kidney disease.[80]

In one study of six older children with a history of AKI not requiring dialysis in the neonatal period, only two were normal; three had CKD, and one was on dialysis. Studies in older children have also shown that AKI leads to CKD in a higher percentage of children than previously appreciated.[75]

MANAGEMENT OF ACUTE AND CHRONIC RENAL FAILURE IN CHILDREN

Preventive Measures

Two studies from different geographic regions of Nigeria demonstrated that the most common cause of AKI in children was volume depletion and that AKI was due to preventable causes.[81,82] Because dialytic resources were scarce, the mortality rate in these studies was quite high.[81,82] On a global scale, the prevention of AKI is likely to have a larger impact on mortality than other measures.

Intravenous infusion of theophylline in severely asphyxiated neonates, given within the first hour after birth, was associated with improved fluid balance, greater creatinine clearance, and reduced serum creatinine levels with no effects on neurologic or respiratory complications.[83-85] Other studies demonstrated improved renal function and decreased excretion of β_2-microglobulin in asphyxiated neonates given theophylline within 1 hour of birth.[83-85] However, the clinical significance of the improved renal function was not clear, and the incidence of persistent pulmonary hypertension was higher in those neonates who had received theophylline.[86] Additional studies are needed to determine the significance of these findings and the potential side effects of theophylline.

Once intrinsic renal failure has become established, management of the metabolic complications of AKI requires meticulous attention to fluid balance, electrolyte status, acid-base balance, and nutrition. Additional renal injury from hypoperfusion and hypoxic/ischemic and nephrotoxic insults that could delay or complicate recovery should be prevented as much as possible.

Similar protective and preventive measures should be used in children with CKD. Adequate therapy for hypertension is critical to preserving renal function in patients with CKD.[87-89] Additional measures to potentially slow the progression of CKD include administration of ACE inhibitors. If nephron numbers are reduced due to congenital or acquired disease, the remaining nephrons undergo hypertrophy and hyperfiltration to compensate for the nephron loss.[87] This overwork of the remnant nephrons results in sclerosis and progression of the renal failure. The hyperfiltration of the remnant nephrons is mediated by the intrarenal generation of angiotensin II, which increases resistance of the efferent arteriole. Therefore, administration of ACE inhibitors can potentially slow the progression of CKD by mechanisms beyond the control of systemic blood pressure.[88] ACE inhibitors have the additional effect of decreasing urinary protein excretion, which is a major factor in the progression of CKD.[88,89] Dietary protein restriction may also slow the progression of CKD, but large-scale studies in adults with CKD have not shown a conclusive benefit.[89] To see a potentially beneficial effect, the protein restriction needs to be substantial, but the protein-restricted diet is not palatable in adults and is potentially too restrictive for growth in children. In contrast, moderate protein restriction is commonly used in pediatric patients to control the BUN and phosphorus levels.

Diuretics and Dopamine

Diuretics and "renal-dose" dopamine are commonly used to prevent or limit AKI. Several clinical studies using mannitol, diuretics, and renal-dose dopamine for AKI have been reported, but none has been conclusive.[90,91] Stimulation of urine output eases management of AKI, but conversion of oliguric to nonoliguric AKI has not been shown to alter the course of renal failure.[92] Mannitol (0.5 to 1.0 g/kg over several minutes) may increase intratubular urine flow to limit tubular obstruction and may limit cell damage by preventing swelling or by acting as a scavenger of free radicals or reactive oxygen molecules. Furosemide (Lasix, 1 to 5 mg/kg per dose) also increases the urine flow rate to decrease intratubular obstruction, and it inhibits the sodium-potassium pump (Na^+,K^+-ATPase), which limits oxygen consumption in already damaged tubules with a low oxygen supply.

The use of "renal-dose" dopamine (0.5 to 3-5 μg/kg/min) to improve renal perfusion after an ischemic insult has become very common in intensive care units (ICUs). Although dopamine increases renal blood flow by promoting vasodilation and may improve urine output by promoting natriuresis, there are no definitive studies to demonstrate that low-dose dopamine is effective in decreasing the need for dialysis or improving survival in patients with AKI.[90-96] In fact, a placebo-controlled, randomized study of low-dose dopamine in adult patients demonstrated that it was not beneficial and did not confer clinically significant protection from renal dysfunction.[93] Other studies showed that renal-dose dopamine is not effective in the treatment of AKI, and one demonstrated that low-dose dopamine worsened renal perfusion and renal function.[96] Three separate meta-analyses showed no benefit of dopamine in AKI.[94,97,98]

Fenoldopam is a potent, short-acting selective dopamine-1 receptor agonist that decreases vascular flow while increasing renal blood flow.[99] A recent meta-analysis of 16 trials concluded that therapy with fenoldopam decreased the incidence of AKI, decreased the need for renal replacement therapy, decreased ICU stay, and decreased death from any cause.[100] These studies were performed only in adult patients, and similar studies are needed in the pediatric setting.

Fluid, Electrolytes, and Acid-Base Balance

Depending on the causes of the AKI or CKD and the presence or absence of associated symptoms such as vomiting or diarrhea, children with AKI or CKD may present with hypovolemia, euvolemia, or fluid overload and pulmonary edema. Because of the rapid onset of AKI, fluid and electrolyte abnormalities are more pronounced, and symptoms develop rapidly. In contrast, the slower evolution of CKD allows for adaptation of the kidney to fluid and electrolyte abnormalities, and biochemical derangements are less apparent for the degree of renal failure compared with AKI. Similarly, symptoms are less apparent in CKD, and many children with CKD are relatively asymptomatic until renal failure is quite advanced.

When one is assessing fluid status, blood pressure, heart rate, skin turgor, and capillary refill are each used to assess the intravascular volume. In children who are intravascularly volume depleted, 10 to 20 ml/kg normal saline solution can be infused to reestablish intravascular volume. If urine output does not increase and azotemia does not improve after fluid resuscitation, then central venous pressure monitoring may be necessary to further guide fluid therapy. If the child presents with fluid overload and does not respond to diuretics, fluid restriction or fluid removal with dialysis or hemofiltration, or both, may be instituted.

Once normal intravascular volume has been reached, euvolemia can be maintained by providing the child with fluid to replace normal water losses from the skin and respiratory and gastrointestinal tracts (insensible losses, 400 $mL/m^2/24\ hr$). Excess stool losses (e.g., from diarrhea) or excess skin and respiratory tract loss (e.g., from hyperthermia) also need to be accounted for and replaced appropriately. Urine losses may be replaced milliliter for milliliter with the appropriate fluid, usually as determined by measuring urine electrolytes. Ongoing fluid therapy is guided by daily weights, blood pressure, accurate fluid input and output records, physical examination, and nutritional needs of the child.

Mild hyponatremia is very common in AKI and may be caused by dehydration, but fluid overload with dilutional hyponatremia is more common. If the serum sodium concentration is greater than 120 mEq/L, fluid restriction or water removal by dialysis or hemofiltration will correct it. If the serum sodium concentration is less than 120 mEq/L, the child is at higher risk for seizures due to hyponatremia, and correction to a sodium level of approximately 125 mEq/L with hypertonic saline solution should be considered. Hypertonic saline is usually infused over several hours to avoid rapid correction of the serum sodium level, which in adults with chronic hyponatremia has been associated with neurologic injury, particularly central pontine myelinolysis.[101] Restriction of free water further corrects hyponatremia.

Because the kidney regulates potassium balance and excretes approximately 90% of dietary potassium intake, hyperkalemia is a common and potentially life-threatening electrolyte abnormality in AKI and CKD. Hyperkalemia results from decreased filtration, impaired tubular secretion, altered distribution of potassium by acidosis that shifts potassium from the intracellular to the extracellular compartment, and release of intracellular potassium due to the associated catabolic state. The serum potassium level may be falsely elevated if the technique of the blood drawing is traumatic, if hemolysis occurs during the blood draw, or if the child has a high WBC or platelet count that can falsely elevate the potassium value.[102] True hyperkalemia results in disturbances of the cardiac rhythm because of its depolarizing effect on the cardiac conduction pathways. The concentration of serum potassium that results in arrhythmia depends on the acid-base balance and the other serum electrolytes. For example, hypocalcemia, which is common in renal failure, exacerbates the adverse effects of the serum potassium on cardiac conduction pathways. Electrophysiologic findings of hyperkalemia include tall peaked T waves and prolongation of the PR interval; flattening of the P waves and widening of the QRS complexes are later abnormalities. Severe hyperkalemia eventually leads to ventricular tachycardia and fibrillation.

Therapy for hyperkalemia is indicated if cardiac conduction abnormalities are noted or if levels are greater than 6 to 7 mEq/L; therapy for hyperkalemia is summarized in Table 46-2. Sodium bicarbonate (0.5 to 1.0 mEq/kg per dose) transfers potassium into cells, but this therapy may precipitate seizures and tetany if the serum calcium level is low, resulting in a decreased ionized calcium level. Intravenous glucose and insulin also transfer potassium from the extracellular to the intracellular compartment.[5,103] Intravenous calcium gluconate increases the threshold potential of the excitable myocardial cells and counteracts the depolarizing effect of the hyperkalemia. Administration of nebulized albuterol acutely lowers the serum potassium level by stimulating intracellular uptake of potassium.[104] Each of these is a temporizing measure and does not remove potassium from the body. Sodium polystyrene sulfonate (Kayexalate) given orally, per nasogastric tube, or per rectum exchanges sodium for potassium in the gastrointestinal tract and results in potassium removal. Complications of this therapy include possible hypernatremia, sodium retention, and constipation. In addition, Kayexalate treatment has been associated with intestinal necrosis in adult postoperative patients.[105] Depending on the degree of hyperkalemia and the need for correction of other metabolic derangements in AKI, hyperkalemia frequently requires the initiation of dialysis or hemofiltration.

Because the kidney excretes net acids generated by diet and intermediary metabolism, acidosis is very common in AKI and CKD. Severe acidosis can be treated with intravenous or oral sodium bicarbonate, oral sodium citrate solutions, dialysis therapy, or some combination of these. It is very important to consider the serum ionized calcium level when determining therapy for acidosis. Approximately half the total calcium is protein bound, and half is free and in the ionized form; the latter concentration is what determines the transmembrane potential and electrochemical gradient. Hypocalcemia is common in AKI, and acidosis increases the fraction of total calcium in the ionized form. Treatment of acidosis can then shift the ionized calcium to a more normal ratio, decreasing the amount of ionized calcium and precipitating tetany or seizures. Therefore, base therapy for acidosis should not be considered without knowledge of the total and ionized

Table 46-2 **Treatment of Hyperkalemia**

Agent	Mechanism	Dose	Onset	Complications
Sodium bicarbonate	Shifts K^+ into cells	1 mEq/kg IV over 10-30 min	15-30 min	Hypernatremia, change in ionized calcium
Albuterol	Shifts K^+ into cells	400 μg by nebulizer	30 min	Tachycardia, hypertension
Glucose and insulin	Shifts K^+ into cells	Glucose 0.5 g/kg, insulin 0.1 U/kg IV over 30 min	30-120 min	Hypoglycemia
Calcium gluconate 10%	Stabilizes membrane potential	0.5-1 mL/kg IV over 5-15 min	Immediate	Bradycardia, arrhythmias, hypercalcemia
Kayexalate	Exchanges Na^+ for K^+ across the colonic mucosa	1 g/kg PO or PR in sorbitol	30-60 min	Hypernatremia, constipation, colonic membrane irritation if given PR

Modified from Andreoli SP. Clinical aspects and management of acute renal failure in children. In: Barratt TM, Avner ED, Harmon WE, eds. *Pediatric Nephrology.* Baltimore: Williams & Wilkins; 1998:1119-1124.

calcium levels. When giving base therapy, administration of 0.5 to 1 mEq/kg over approximately 1 hour is reasonable. Administration of sodium bicarbonate generates carbon dioxide, and an intact respiratory system to excrete the excess generated CO_2 is required for bicarbonate therapy to be effective.

Calcium Balance, Phosphate Balance, and Renal Osteodystrophy

Because the kidney excretes a large amount of ingested phosphorus, hyperphosphatemia is a very common electrolyte abnormality in patients with AKI or CKD. Hyperphosphatemia should be treated with dietary phosphorus restriction and administration of oral calcium carbonate or other calcium compounds to bind phosphorus and prevent gastrointestinal absorption of phosphorus.[106,107] Aluminum-containing compounds should be avoided, because several studies have demonstrated that orally administered aluminum-containing phosphorus binders result in substantial aluminum absorption, leading to severe aluminum intoxication.[108,109]

The cause of hypocalcemia in AKI and CKD is multifactorial and may involve hyperphosphatemia, inadequate gastrointestinal calcium absorption due to inadequate 1,25-vitamin D production by the kidney, and skeletal resistance to the action of parathyroid hormone.[110,111] As described previously, acid-base balance has a profound effect on the level of ionized calcium, and interpretation of the calcium level and consideration of therapy need to take into consideration the degree of acidosis. If hypocalcemia is severe or if bicarbonate therapy is necessary for hyperkalemia, therapy with 10% calcium gluconate (100 mg/kg up to a maximum of 1 g, or 1 mL/kg up to a maximum of 10 mL) should be given over 30 to 60 minutes with continuous electrocardiographic monitoring. Hypocalcemia may also be treated by oral administration of calcium carbonate or other calcium salts.

Renal osteodystrophy is an important complication of CKD and contributes to substantial morbidity.[100,101] Bone disease is almost universal in patients with CKD; in many children symptoms are minor to absent, but others may develop bone pain, skeletal deformities, and slipped epiphyses. High-turnover bone lesions are associated with secondary and tertiary hyperparathyroidism, whereas low-turnover bone disease (also called adynamic bone disease) is associated with aluminum intoxication and suppressed parathyroid activity.[110,111] The pathogenesis of hyperparathyroid bone disease is multifactorial and is related to phosphate retention, decreased synthesis of 1,25-vitamin D, decreased intestinal absorption of calcium, increased parathyroid gland activity, and alterations in the calcium-sensing receptor. Severe hyperparathyroid renal osteodystrophy can result in subperiosteal erosions and "brown tumors" characteristic of advanced hyperparathyroidism (Fig. 46-2). Treatment includes control of serum phosphorus and calcium supplementation as described previously, avoidance of aluminum-containing antacids, and administration of oral or intravenous calcitriol in appropriate doses depending on the type of bone disease.

Anemia

Anemia in AKI may be related to hemolysis (e.g., in HUS), whereas anemia in CKD is a result of deficiency of erythropoietin, which is produced by the kidney. Iron-deficiency anemia and decreased red blood cell survival may also play a role in the anemia of CKD. Human recombinant erythropoietin has been available since the late 1980s and has dramatically changed the care of patients with CKD and end-stage renal disease. Symptoms of anemia can be avoided, exposure to blood-borne pathogens reduced, and sensitization to human leukocyte antigens minimized by therapy with erythropoietin. Therapy is started when the hematocrit is approximately 30%, or earlier if the patient is symptomatic. The starting dose is approximately 50 U/kg per dose, administered one to three times a week. The dose can be incrementally increased to achieve the target hemoglobin concentration. Erythropoietin may be given intravenously or subcutaneously, but the subcutaneous route may be more effective because it allows prolonged absorption and slower clearance of the hormone.[112] The child usually requires concomitant iron therapy so that the erythropoietin therapy will be effective.

Growth Failure

Growth failure is a very common complication of CKD and is the presenting symptom in some cases. Among a large cohort of children with CKD who had a mean creatinine concentration of 2.4 mg/dL, the average height was 1.5 standard deviations (SD) below age- and gender-specific norms.[113] The mechanisms of growth failure are complex and multifactorial; poorly controlled renal osteodystrophy, inadequate nutrition, chronic acidosis, and abnormalities of the growth hormone axis are major contributors to poor growth in the child with CKD.[107] Despite adequate nutrition and good control of bone disease and acid-base balance, many children remain substantially growth retarded.

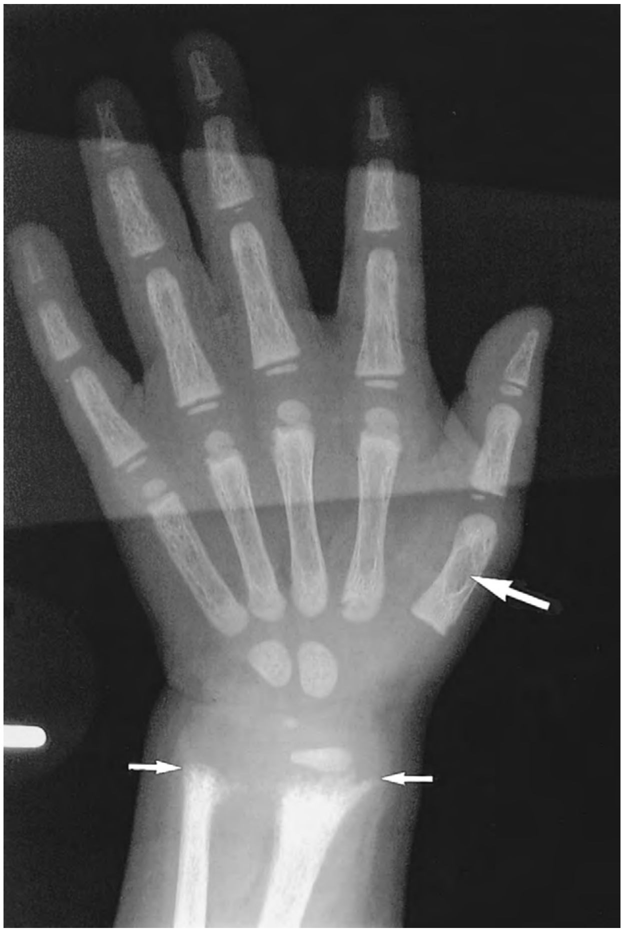

Figure 46-2 Radiograph of the hand of a 2½-year-old girl with chronic renal failure due to a neurogenic bladder. The radiograph demonstrates a coarse trabecular pattern of all bones, with acrosteolysis of the distal phalanges and subperiosteal resorption of the phalanges. There is severe fraying of the distal radial and ulnar metaphysis *(smaller arrows)*, and a cystic lesion is present in the first metacarpal *(large arrow)*, suggestive of a "brown tumor" resulting from severe hyperparathyroidism.

Therapy with human recombinant growth hormone has been approved for use in children with CKD and has been shown to accelerate growth, induce persistent catch-up growth, and lead to normal adult height.[114] Indications for growth hormone therapy include a height SD score less than 3% or a declining growth velocity.[107] Complications of growth hormone therapy are rare but may include glucose intolerance, hyperinsulinemia, pseudotumor cerebri, exacerbation of poorly controlled renal osteodystrophy, and perhaps a detrimental effect on renal function with progression of glomerulosclerosis or acute rejection in the child who has received a kidney transplant.[115,116] However, recent studies have demonstrated that long-term administration of growth hormone is safe and is not associated with acute rejection.[117]

Medications

Pharmacotherapy in AKI and CKD requires careful attention to the metabolic elimination of the drug and adjustments for the degree of renal failure. Many drug adjustment tables are based on the glomerular filtration rate (GFR) (i.e., for patients with >50, 20 to 50, or <20 mL/min/1.73 m^2 GFR). It is important to estimate the child's level of renal function appropriately and to consider the rate of increase of the serum creatinine rather than the absolute creatinine level. To prevent further insults to the kidney, it is best to avoid nephrotoxic drugs in AKI, but if they are needed, it is appropriate monitor drug levels and potentially adverse effects.

Hypertension

Hypertension in AKI and CKD may be related to volume overload or to alterations in vascular tone or both. If hypertension is related to volume overload, then fluid removal with dialysis or hemofiltration is necessary if diuretic therapy is not sufficient. Depending on the degree of blood pressure elevation and the origin of the hypertension, antihypertensive therapy may also be indicated.[118] The choice of antihypertensive therapy depends on the degree of blood pressure elevation, the presence of central nervous system symptoms of hypertension, associated conditions, and the cause of the AKI or CKD. For the child who has severe hypertension or is encephalopathic, intravenous therapy with nicardipine or nitroprusside (beginning dose, 0.5 to 1.0 μg/kg/min) is indicated, with monitoring of serum levels of thiocyanate, a metabolic product of nitroprusside that is excreted by the kidney. Alternative therapies include intravenous labetalol (0.25 mg/kg), or enalaprilat. Intravenous hydralazine or sublingual nifedipine can be used for less severe hypertension. Once the blood pressure is controlled, treatment with oral long-acting agents can be initiated.

As described previously, ACE inhibitors can delay the progression of CKD by an effect that is independent of reduction of systemic blood pressure. However, renal function and electrolytes need to be monitored in a child receiving ACE inhibitors, because inhibition of the generation of angiotensin II can alter internal hemodynamics, leading to a decreased creatinine clearance and elevation of the serum creatinine concentration. In addition, inhibition of angiotensin II decreases the generation of aldosterone, with the subsequent development of hyperkalemia.[118]

Nutritional Therapy

AKI and CKD can be associated with severe anorexia, and malnutrition can develop rapidly. Proper nutrition is essential in the management of AKI and CKD. If the gastrointestinal tract is intact and functional, enteral feedings with formula (PM 60/40 for newborns and infants) should be instituted as soon as possible. In older children, a diet of foods with high-biologic-value protein, low phosphorus, and low potassium can be used. Infants should receive maintenance calories (120 kcal/kg/day), and older children should receive appropriate maintenance calories or higher if needed because of the catabolic state and malnutrition. If the child is oliguric or anuric and sufficient calories cannot be achieved while maintaining appropriate fluid balance and growth, earlier initiation of dialysis should be considered.

RENAL REPLACEMENT THERAPY

The purpose of renal replacement therapy is to remove endogenous and exogenous toxins and to maintain fluid, electrolyte, and acid-base balance until renal function improves (if the patient has AKI) or until transplantation can be achieved (in those with CKD). Renal replacement therapy may be provided by peritoneal dialysis (PD), intermittent hemodialysis (HD), or hemofiltration with or without a dialysis circuit (hemofiltration is used only in AKI). There are no studies in children and few studies in adults comparing outcomes with different renal replacement therapies in the treatment of AKI and CKD.[119,120] Many factors, including the age and size of the child, the cause of renal failure, the degree of metabolic derangement, blood pressure, and nutritional needs, are considered in deciding when to initiate renal replacement therapy and which form to choose.[107] Table 46-3 highlights the relative advantages and disadvantages of each modality. During AKI, it is important to initiate renal replacement therapy in a timely manner; initiation when the child has severe fluid overload has been associated with increased mortality.[121,122]

The indications for initiation of renal replacement therapy are not absolute and take into consideration a number of factors, including the cause of renal failure, the rapidity of the onset of renal failure, the severity of fluid and electrolyte abnormalities, and the age of the child. Because infants and younger children have less muscle mass than older children, they require initiation of renal replacement therapy at lower serum levels of creatinine and BUN. The presence of fluid overload unresponsive to diuretic therapy and the need for enteral feedings or hyperalimentation to support nutritional needs are important factors in considering the initiation of renal replacement therapy. Other indications for the initiation of chronic dialysis include fatigue, anorexia, and poor school attendance.

Peritoneal Dialysis

PD has been a major modality of therapy for AKI and CKD, particularly in neonates and small children.[107,123-125] It is frequently used in such patients when vascular access is difficult to maintain. Advantages of PD are that it is relatively easy to perform, it does not require heparinization, and the child does not need to be hemodynamically stable. The disadvantages include a slower correction of metabolic parameters and the potential for peritonitis. To increase the efficiency of PD, frequent exchanges (as often as every hour) and use of dialysates with higher glucose concentrations are used to remove more solute and more water, respectively. Relative contraindications include recent abdominal surgery and massive organomegaly or intra-abdominal masses as well as ostomies, which may increase the risk of peritonitis. Continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis, also called continuous cycling peritoneal dialysis (CCPD), are the most common forms of dialysis therapy used in children with CKD.[107,123-126] CAPD/CCPD allows for home care, normal school attendance, continuous control of metabolic parameters, freedom from complex machinery, and less severe dietary restriction.

Access to the peritoneal cavity is usually through a Tenckhoff catheter. Older children can initiate PD with volumes of 15 to 20 mL/kg body weight, whereas neonates and infants usually need slightly lower volumes of 5 to 10 mL/kg body weight. The dialysate volume can be increased to a maximum of 50 mL/kg, depending on the need for additional solute and fluid removal, the clinical needs of the child, and the respiratory status of the child. The electrolyte concentration of dialysate is similar to that used for chronic dialysis and contains lactate 30 to 40 mEq/L. If the child has lactic acidosis, dialysis with standard solutions will increase the lactate load and aggravate the acidosis. PD with a bicarbonate-buffered dialysate solution should be considered in the child with lactic acidosis.

Substantial fluid and electrolyte imbalances can occur during PD, especially when frequent exchanges are used, whereas prolonged use of hypertonic glucose solutions can result in hyperglycemia, hypernatremia, and hypovolemia. Peritonitis (dialysate WBC count >100/mm^3) is another complication of acute PD that can be treated with intraperitoneal antibiotics in a manner similar to that for peritonitis occurring during chronic PD. Repeated episodes of peritonitis can lead to membrane injury and ultimately to membrane failure.[125,126] If the child develops hypokalemia or hypophosphatemia during the course of dialysis, then 3 to 4 mEq/L of potassium chloride or 2 to 3 mEq/L potassium phosphate can be added to the dialysate. To avoid hypothermia, particularly in neonates, infants, and small children, the dialysate should be warmed to body temperature before infusion into the peritoneal cavity.

Hemodialysis

HD has also been used in the treatment of AKI and CKD during childhood.[127-129] HD has the advantage that metabolic abnormalities can be corrected rather quickly and hypervolemia

Table 46-3 **Comparison of Renal Replacement Therapies**

Parameter	Peritoneal Dialysis	Hemodialysis	CVVHD
Solute removal	Good	Excellent	Fair (excellent)
Fluid removal	Good	Excellent	Excellent (excellent)
Need for hemodynamic stability	No	Yes	No (no)
Hyperkalemia treatment	Fair	Excellent	Poor to fair (excellent)
Ease of access	Not difficult	Difficult	Difficult (difficult)
Continuous treatment	Yes	No	Yes (yes)
Need for anticoagulation	No	Usually	Variable (variable)
Possible respiratory compromise	Moderate	Low	Low (low)
Risk for peritonitis	High	No	No (no)
Precipitation of hypotension	Low	High	Moderate (moderate)
Disequilibrium	No	High	Low (moderate)
Specifically trained staff	Moderate	High	High (high)

CVVHD, continuous venovenous hemodiafiltration.

can be corrected by rapid ultrafiltration as well. The disadvantages of HD include the requirement for heparinization, the need for maximally purified water supplied by a reverse osmosis system, and the need for skilled nursing personnel. Relative contraindications include hemodynamic instability or severe hemorrhage. If HD is needed in a child who has active hemorrhage or is at high risk of hemorrhage, regional heparinization, citrate anticoagulation, heparin-free dialysis, or some combination of these can be used to minimize the risk of hemorrhage.

During HD, rapid ultrafiltration may also lead to hypotension, which has been shown to result in additional renal ischemia and to potentially prolong an episode of AKI.[130] Rapid removal of BUN and other uremic products can result in dialysis disequilibrium, particularly if the child begins HD with a high level of BUN (>120 to 150 mg/dL). The pathogenesis of this syndrome is complex and multifactorial but may be related to rapid removal of urea from the blood while brain levels decline more slowly, resulting in disequilibrium. Symptoms include restlessness, fatigue, headache, nausea, vomiting leading to confusion, seizures, and coma.[131] Mannitol can be used during HD to offset the alteration in osmolality that results from lowering the BUN.

Vascular catheters can be placed in the internal or external jugular veins or in the femoral vein. To avoid hypotension, the total volume of the dialysate circuit, including the dialyzer and tubing, should not exceed 10% of the child's blood volume. Another important consideration in HD treatment of a child with AKI or CKD is the choice of a dialysis membrane. Several studies in adults have shown that cuprophane membranes are bioincompatible and activate complement and PMNs to degranulate, produce reactive oxygen molecules, and initiate the generation of proinflammatory cytokines.[132-134] The generation of these toxic products results in additional systemic and renal injury, potentially prolonging the course of AKI and promoting deterioration of residual renal function in patients with CKD.[132-134]

Hemofiltration

Renal replacement therapy for AKI with hemofiltration including continuous venovenous hemofiltration (CVVH), or with the addition of a dialysis circuit to the hemofilter, known as continuous venovenous hemodiafiltration (CVVHD), has become increasingly popular for the treatment of AKI during childhood.[107,135-139] Hemofiltration without dialysis (CVVH) follows the principle of removal of large quantities of ultrafiltrate from plasma and their replacement with an isosmotic electrolyte solution; hemofiltration with dialysis (CVVHD) also results in solute removal via the added dialysis circuit.

The advantages of hemofiltration (with or without a dialysis circuit) are that it can result in rapid fluid removal, that it does not require the patient to be hemodynamically stable when a pump is inserted into the circuit, and that it is continuous, avoiding the rapid solute and fluid shifts that occur in hemodialysis. The disadvantages are that hemofiltration may require constant heparinization and that there is a potential for severe fluid and electrolyte abnormalities owing to the large volume of fluid removed and subsequently replaced. Hemofiltration is typically used in children who are hemodynamically unstable, have multiorgan dysfunction, and require pressor support; therefore, it is not surprising that the survival of children with AKI treated with hemofiltration is less than with other modalities.[135-142]

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CHAPTER 47

PEDIATRIC RENAL TRANSPLANTATION: MEDICAL AND SURGICAL ASPECTS

Jens Goebel, William DeFoor, and Curtis Sheldon

The outcome of pediatric renal transplantation has advanced tremendously since the 1980s. Historically, management of end-stage renal disease (ESRD) in children was met with tremendous pessimism. In 1964, Riley[1] expressed the fear that "continued growth retardation would lead to the kidney being based in a healthy dwarf." In 1979, Reinhart[2] suggested that "the cost to the child of physical and emotional discomfort" would limit the application of this treatment. Despite this inauspicious inception, advances in the survival of patients and grafts, and improvements in the patients' quality of life have enabled renal transplantation to become the optimal form of management of pediatric ESRD, and only a few contraindications exist for this therapeutic modality (Table 47-1).

Advancements in immunosuppression, surgical techniques, and nutrition, and the administration of growth hormone and erythropoietin have enabled several centers to establish successful pediatric renal transplantation programs. Contributions to the science of renal transplantation in children have been thwarted by the small patient populations available to individual centers. The application of new treatment modalities, which have developed so rapidly in adult transplantation programs, has been difficult to assess in children because of the slower accumulation of data possible in any individual program. This limitation has been addressed by the development of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) in 1987, which allows the accumulation of information from large numbers of patients from multiple centers into study protocols, enabling the generation of meaningful and usable data sets.

The discipline of renal transplantation is pertinent to the pediatric urologist for numerous reasons. Urologic diseases (e.g., obstructive uropathy and renal aplasia/hypoplasia/dysplasia) cause more than 30% of all chronic kidney disease (CKD) and ESRD in children, making them the most common etiology of ESRD in this age group (Table 47-2). Consequently, and as detailed in a subsequent section, the pediatric urologist is often required for pretransplantation evaluation and preparation: Nephrectomy may be required for conditions predisposing to infection and renal-derived hypertension. Structural and functional abnormalities of the bladder, refractory to medical management, may require reconstruction. Ureteral reconstruction for severe reflux or obstructing megaureter or for urinary undiversion may be necessary. In addition, surgically derived access for intermittent catheterization may be necessary. Urologic input is often needed for key elements of post-transplantation care, such as monitoring of bladder function, evaluation of allograft dysfunction, and management of urinary tract infection (UTI) or ureteral complications. Finally, the tremendous advances in transplantation science have significant application to important pathophysiologic processes pertinent to the practice of pediatric urology, such as the molecular mechanisms responsible for renal injury in general[3-6] and embryogenesis.[7]

Pediatric urology and related disciplines are greatly indebted to the transplantation scientists whose work has proved to have such wide-reaching medical implications. We are particularly indebted to pediatric nephrologists, who have furthered understanding of the pathophysiology and implications of renal insufficiency, who provide the medical support that enables children with ESRD to be maintained and stabilized until transplantation, and who contribute so intensely to the perioperative and long-term management of transplant recipients. Additionally, the data accumulation and management coordinated by NAPRTCS[8] and the United Network for Organ Sharing[9] have been instrumental to the formation of successful pediatric transplantation protocols.

The magnitude of the challenge created by ESRD care is illustrated in the public database of the Organ Procurement and Transplantation Network (www.optn.org, February 2007): As of February 2007, the number of patients in the United States awaiting a kidney from a deceased donor had grown to almost 70,000, owing in part to the addition of 25,000 to 30,000 new patients to the wait-list annually between 2004 and 2006. In contrast, less than 10,000 such kidneys became available for transplantation in each of those years. Approximately 3% of newly wait-listed patients are children; the number of pediatric renal transplantations performed each year has remained relatively constant because the number of living kidney donors for pediatric recipients has not increased significantly. In parallel, more recent enhancements in the preferential allocation of kidneys from deceased donors to pediatric recipients are just beginning to be followed by a relative increase in transplants from such donors for children. Children received more kidneys from deceased donors than from living donors in 2005 and 2006, representing a reversal of the traditional predominance of living donors for pediatric recipients. Preliminary observations suggest that the above-mentioned enhancements in the preferential allocation of deceased donor kidneys to children also decreased the waiting time until transplantation for wait-listed children, at least if they were not highly sensitized (see later).

MANAGEMENT OF CHILDREN WITH CHRONIC KIDNEY DISEASE

Medical Aspects

CKD has been classified into stages with associated recommendations for medical interventions, and this approach has been adapted for children (Table 47-3).[10] Pediatric CKD can have unique and devastating effects on growth and development.[11] Although the availability of recombinant human growth hormone (rhGH) has had a huge impact, linear growth retardation is an almost universal consequence of advanced CKD in children.[12,13] Many factors have been implicated in this growth retardation, such as malnutrition, renal osteodystrophy, sodium wasting, metabolic acidosis, hormonal disturbances, and anemia.

Growth retardation in pediatric ESRD has been extensively reviewed.[14] Before the availability of rhGH, approximately 30% to 40% of children with ESRD were below the

Table 47-1 Contraindications to Transplantation*

Malignancy
Chronic persistent infection
Recalcitrant noncompliance
Ongoing substance abuse
Severe irreversible extrarenal disease, including psychiatric illness
Absent insurance or equivalent coverage

*Contraindications are potentially modifiable: "Safe" time periods after curative treatment for malignancy are available in the literature; some centers offer kidney transplantation to certain patients infected with human immunodeficiency virus; noncompliance and substance abuse can be overcome in some instances; and, in the authors' experience, financial coverage can eventually be established in virtually all cases.

Table 47-2 Most Frequent Indications for Kidney Transplantation in Adults and Children

Adults		Children	
Indication	**%**	**Indication**	**%**
Diabetes	27.1	Agenesis/dysplasia	15.9
Glomerular disease	21.5	Obstructive uropathy	15.8
Hypertension	21.4	Focal segmental sclerosis	11.7
Failed previous graft	11.4	Failed previous graft	9.3

Adapted from the 2005 Annual Report of the OPTN and the 2006 Annual Report of NAPRTCS.

Table 47-3 Chronic Kidney Disease (CKD) Stages and Glomerular Filtration Rate (GFR) in Children

Panel A: National Kidney Foundation Kidney Disease Outcome Quality Initiative Classification of the Stages of CKD

Stage	GFR (mL/min/1.73 m^2)	Description	Action Plan*
1	≥90	Kidney damage with normal or increased GFR	Treat primary and comorbid conditions Slow CKD progression, cardiovascular disease risk reduction
2	60-89	Kidney damage with mild reduction of GFR	Estimate rate of progression of CKD
3	30-59	Moderate reduction of GFR	Evaluate and treat complications
4	15-29	Severe reduction of GFR	Prepare for kidney replacement therapy
5	<15 (or dialysis)	Kidney failure	Kidney replacement therapy

*The actions that are listed in the more severe stages of CKD also include actions from less severe stages.

Panel B: Normal GFR in Children and Adolescents

Age (Sex)	Mean GFR ± SD (mL/min/1.73 m^2)
1 wk (boys and girls)	41 ± 15
2-8 wk (boys and girls)	66 ± 25
>8 wk (boys and girls)	96 ± 22
2-12 yr (boys and girls)	133 ± 27
13-21 yr (boys)	140 ± 30
13-21 yr (girls)	126 ± 22

Panel C: Estimation of GFR in Children Using Serum Creatinine and Height

Reference (No. Subjects)	Equation
Schwartz et al ($N = 186$)	$C_{Cr}(mL/\min/1.73m^2) = \dfrac{0.55 \times Height\,(cm)}{S_{Cr}(mg/dL)}$

C_{Cr}, creatinine clearance; S_{Cr}, serum creatinine. In the Schwartz equation, the constant to be used in young children (<1 year old) is 0.45; in adolescent boys, the value of the constant changes to 0.7. To convert serum creatinine in μmol/L to mg/dL, the value in μmol/L is multiplied by 0.0113.

Adapted from Hogg RJ, Furth S, Lemley KV, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. *Pediatrics.* 2003;111(6 Pt 1):1416-1421.

3rd percentile for height before the onset of dialysis. Growth velocity below the 3rd percentile was noted in almost 70% of children on hemodialysis. Prepubertal children on dialysis for more than 1 year had a mean relative height loss of approximately 0.4 SD per year. One third lost more than 0.5 SD per year. After 5 or more years on dialysis, prepubertal children lost an average of 2.4 SD in height compared with 0.4 SD after transplantation.

Emphasis on nutritional support; correction of acidosis, anemia, and electrolyte disturbances; and, most importantly, rhGH have significantly improved linear growth such that children who receive a kidney transplant now achieve greater height (Fig. 47-1A). The most advantageous event in maximizing growth in young children with ESRD is renal transplantation because significant catch-up growth is possible in children receiving transplants before age 6 years, but becomes notably blunted in older children (Fig. 47-1B). In addition to age at transplantation, other important variables influencing post-transplantation growth include the pretransplantation growth deficit; the function of the graft; and the use of alternate-day steroid maintenance therapy, complete steroid withdrawal; or primary steroid avoidance.[15-20] The use of rhGH therapy in the recipient is another strategy enabling improvement in growth velocity.[21-23]

Neurologic development also is affected by chronic renal insufficiency.[24] The brain seems to be most vulnerable to uremia and malnutrition during the first 2 years of life, as reflected by diminished head circumference and diminished ultimate intellectual performance. Historically, approximately 95% of patients developing ESRD in the first year of life show developmental delay, with hypotonia, seizure activity, and dyskinesia noted in 65%, 65%, and 55%.[25] Infants with ESRD have a normal head circumference at birth. By 1 year of age, this parameter declines, however, to 2 and 3 SD below the mean in 75% and 50% of patients.[26] Renal transplantation in infancy has the potential to improve ultimate neurologic development as measured by head circumference and mental and motor function.[27] Developmental delay has been noted in 85% of children on long-term dialysis compared with 31% of children with a functioning allograft.[28] More recent improvements in the overall management and specifically in dialysis therapy for infants and very young children seem to offer better outcomes in this age group,[29] however, and allow delay of renal transplantation until it is less difficult and risky, typically by the time a patient weighs 8 to 10 kg.

Additional common consequences of advanced CKD include hypertension; renal osteodystrophy; and secondary hyperparathyroidism, metabolic acidosis, and anemia.[10,30-32] Successful management of these problems before transplantation often requires a complex combination of medications, dietary restrictions and supplemental feedings, and sometimes eventually long-term dialysis, creating marked challenges and restrictions with regards to patients' and families' quality of life, compliance, finances, and issues such as school attendance.

Urologic Aspects

The potentially devastating adverse influences of uremia on the developing child have important implications for the pediatric urologist, who is often the first specialist involved in the management of young children with severe renal injury. Early intervention is essential to maximize the outcomes. Delays and errors in early management are particularly detrimental. The pediatric urologist should vigilantly monitor patients at risk for ESRD for evidence of deterioration of renal function and for growth retardation, developmental delay, anemia, acidosis, and hypertension. Early recognition of the onset of significant renal insufficiency is essential, with prompt involvement of the pediatric nephrologist and attention directed at nutrition, correction of acidosis, maintenance of red blood cell mass (erythropoietin), stabilization of bone density (vitamin D), maximization of growth (rhGH), control of hypertension and proteinuria, and application of dialysis when indicated. Additionally, aggressive urologic intervention is indicated to maximize the extent and duration of the contribution of native renal function. Interventions should be designed to minimize adverse affects on subsequent dialysis and transplantation management.

Perhaps the greatest impediment to the development of organized pediatric ESRD care and particularly to pediatric renal transplantation has been the reluctance to recognize the tremendous differences between children and adults.[12,13] In addition to the relative urgency of attaining an allograft with respect to such considerations as growth and neurologic development, the etiology of ESRD is dramatically different in that approximately 30% of pediatric patients have significant urologic concerns (see Table 47-2).[33] Also, many children with such entities as renal dysplasia have significant underlying bladder dysfunction pertinent to the pediatric urologist.

There has been a tendency to take a fatalistic view of urologic intervention in children whose primary urologic disease is complicated by renal insufficiency. Although it is true that the ultimate incidence of ESRD may not be altered, early intervention may enable the adverse effects of uremia on growth and development to be positively affected, allowing the onset of dialysis and transplantation to be delayed. This delay is important because these modalities may be applied more safely and successfully in older children.

Elevated bladder pressures have an adverse impact on upper urinary tract integrity.[11] Detrusor instability and detrusor-sphincter dyssynergy increase the risk of UTI, vesicoureteral reflux (VUR),[34] and failure of antireflux surgery.[35] Conversely, treatment with oxybutynin to decrease intravesical pressure has the potential to reduce the incidence of UTI and VUR.[36] Upper tract deterioration in children with neurogenic bladder has been shown to be correlated with intravesical pressures exceeding 40 cm H_2O.[37,38] In the setting of chronic retention, renal pelvic and bladder pressures closely correspond even in the absence of VUR,[39] and the critical pressure of 40 cm H_2O correlates the onset of renal papillary morphologic distortion with the onset of intrarenal reflux of urine.[40] Additionally, an association between infravesical obstruction, intravesical pressure, and renal injury may be inferred from the protective influences of "pop-off" mechanisms occasionally encountered in infants with posterior urethral valves.[41]

Some series have documented diminished survival and function of renal allografts after transplantation into the valve bladder.[42,43] That this association is not simply due to the presence of an irregular distorted bladder with stasis is suggested by the observation that kidneys transplanted into Eagle-Barrett (prune-belly) syndrome bladders did not experience a similar reduction in allograft survival or function.[44] Our renal allograft survival data are comparable between patients with a valve bladder and a control group of ESRD patients with no voiding dysfunction.[45]

The critical pathophysiologic interrelationship between the dysfunctional bladder and the sequelae of renal deterioration is perhaps best illustrated by the management of an infant with posterior urethral valves. Although this interrelationship is postulated, it has been difficult to accumulate data that show an influence of bladder management on subsequent growth and development. This is due primarily to the length of follow-up required and the absence of controlled series. It is possible, however, to infer an influence based on urinary

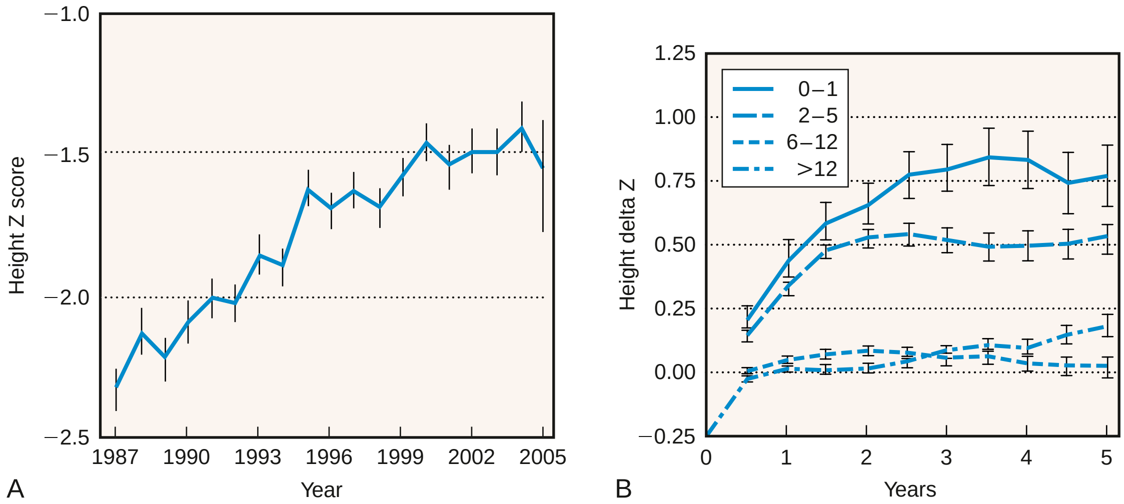

Figure 47-1 Height *z* score of children at the time of transplantation by transplant year **(A)** and change in *z* score after transplantation by age group **(B).** Height *z* scores are calculated by dividing the difference between the patient's height and the 50th height percentile for the patient's age by the standard deviation of height for the patient's age. (From the 2006 NAPRTCS Annual Report.)

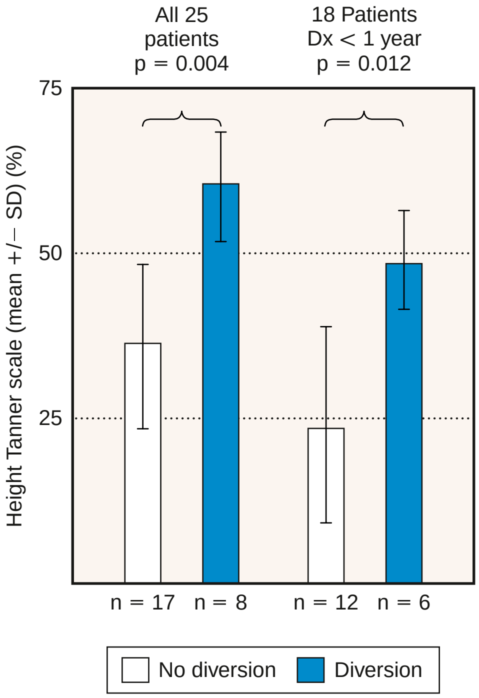

Figure 47-2 Effect of urinary diversion on height at 10 years of age in posterior urethral valve patients. Dx, diagnosis. (Redrawn from Lyon RP, Marshall S, Baskin LS. Normal growth with renal insufficiency owing to posterior urethral valves: value of long-term diversion: a twenty-year follow-up. *Urol Int.* 1992;48:125-129.)

diversion data. Lyon and colleagues[46] compared 8 patients with posterior urethral valves managed by urinary diversion with 17 patients managed without urinary diversion. Long-term follow-up data were available, and the populations were similar with respect to hydronephrosis, reflux, azotemia, and the incidence of ultimate transplantation. Analysis of height measurements showed a statistically significant positive influence of diversion on ultimate height in the overall group and in the 18 patients who were diagnosed younger than 1 year (Fig. 47-2).

These data do not show that urinary diversion is superior to management methods that do not include diversion because huge advances in infant valve bladder management have developed since the 1970s. Although the number of patients is small, these data strongly suggest that an ultimate improvement in clinical outcome may be attained by early, aggressive attention to maintaining safe intravesical pressures—even in patients whose renal injury is sufficient ultimately to result in ESRD. Such patients must be conceptualized and managed according to established urodynamic principles. Critical parameters include compliance (pressure and volume), postvoid residual (PVR), voiding pressure, and leak point pressure. An important clinical urodynamic parameter is urinary output volume. This factor is often overlooked, but can become crucial in an azotemic child with a high urine volume owing to a concentrating defect.

Another consideration favoring aggressive urologic management of the valve bladder is the maturation of bladder function that may spontaneously occur with age. Figure 47-3 shows the effect of age on bladder compliance in the ESRD valve bladder. It is evident that the valve bladder in a young child is generally operating at high pressure and low compliance. In contrast, an older child tends to have a larger capacity, low-pressure bladder that may require intermittent catheterization to empty. As the patient develops from a high pressure bladder to myogenic failure, a period of balanced voiding may be achieved. Urinary diversion by cutaneous vesicostomy or cutaneous ureterostomy or pyelostomy has no effect on this maturation process, having no discernible negative impact on the ultimate capacity or compliance. Consequently, it is unusual to encounter an ESRD valve patient older than 5 years who has required augmentation. Younger valve patients have occasionally required pretransplantation augmentation. The ability to defer transplantation by maintaining native renal function can simplify care significantly, and avoid the potential complications of augmentation in this challenging setting.

Figure 47-4 illustrates a physiologic approach to a patient with threatened or injured upper tracts and a dysfunctional bladder, such as is seen with the posterior urethral valve bladder—even after effective fulguration of valve tissue. A typical pressure-volume relationship is shown (*curve a*). The exact portion of the curve at which the patient is operative depends

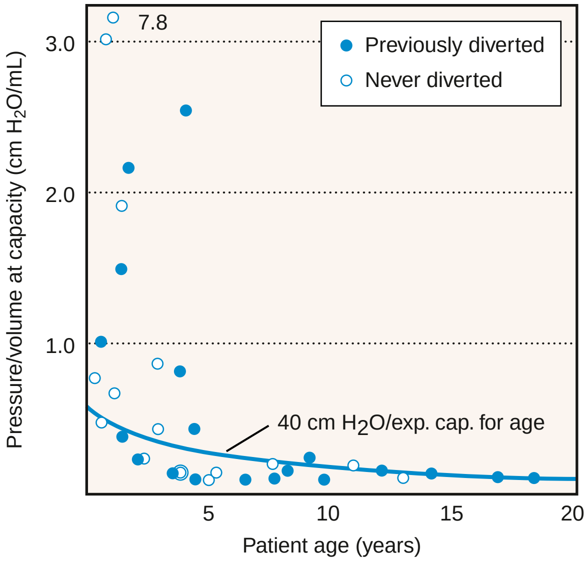

Figure 47-3 Relationship of valve bladder compliance characteristics versus age. The line indicates the ratio of 40 cm H_2O divided by the expected bladder capacity for age.

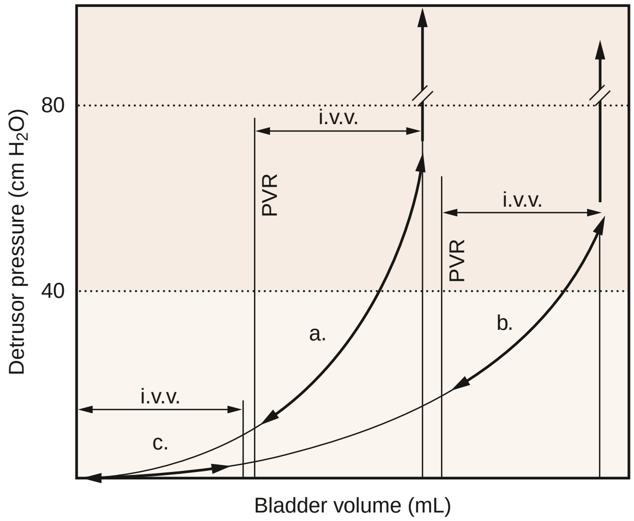

Figure 47-4 Conceptual approach to the management of the dysfunctional bladder associated with renal injury (see text). i.v.v., incremental voided volume; PVR, postvoid residual.

on the PVR, the urinary output (mL/hr), and the elapsed time between voids. During the filling phase, pressure increases with volume until a threshold pressure is attained that risks renal injury (*shaded area*). Voiding results in an abrupt and detrimental increase in pressure. The incremental voided volume (*i.v.v.*) is indicated by the *horizontal double arrow,* which for purposes of illustration is held constant. The incremental voided volume is determined by the elapsed time between voiding (or catheterization) and by the urine output. The effective PVR is determined by the bladder's ability to empty and by reflux, which displaces bladder volume (during filling and voiding) into the upper tracts. On completion of voiding, this urine immediately returns to the bladder.

The compliance curve may be altered medically by the administration of oxybutynin chloride or surgically by bladder augmentation (*curve b*). The detrusor pressure may be dramatically reduced for a given intravesical volume. This intervention may also result in an increase in the PVR, however. Consequently, although the working pressure range is improved, it is still deleterious. Voiding results in a further increase in detrusor pressure. The pressure characteristics can be dramatically improved by the addition of intermittent catheterization (*curve c*). Here, the PVR is eliminated, as is the incremental voiding pressure. The risk of infection is lessened, and the pressure curve is entirely within the safe range. In an older and compliant child, a less dramatic but often totally satisfactory improvement can be obtained by frequent timed double voiding. Approximating a satisfactory working pressure range (*curve c*) allows a maximal duration of significant native renal function, delays ESRD, potentially reduces the developmental sequelae of uremia, and ensures a safe receptacle for the allograft ureter when transplantation is needed.

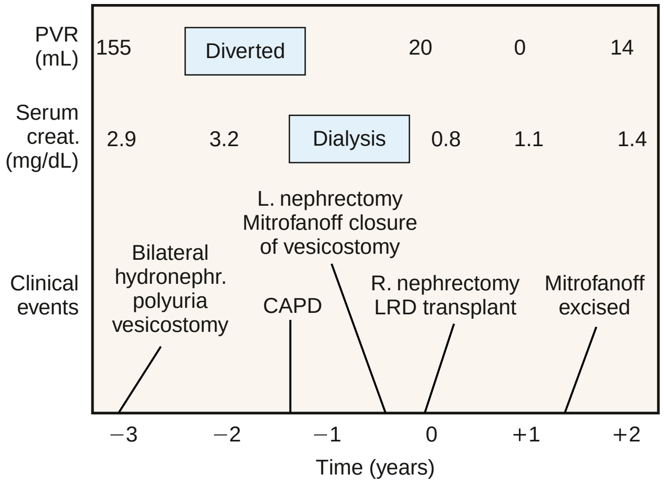

Figure 47-5 Clinical course of a patient with primary renal disease (cystinosis) and severe polyuria who developed hydronephrosis and bladder decompensation necessitating intermittent catheterization. After bilateral native nephrectomy, transplantation, and normalization of urine output, bladder function normalized. CAPD, chronic ambulatory peritoneal dialysis; LRD, living related donor; PVR, postvoid residual.

A fixed, high urine output from a concentrating defect can have an extremely detrimental effect on the bladder. Figure 47-5 illustrates the clinical course of a boy with ESRD from cystinosis. His bladder was gradually distorted because he could not empty his bladder frequently enough to compensate for his polyuria, resulting in progressive enlargement and ultimate decompensation of his bladder and, subsequently, hydronephrosis. Ultimately, he could not empty his large, flaccid bladder. Intermittent catheterization was initiated, which he did not tolerate, and a vesicostomy was performed. He was referred for transplantation, at which point the vesicostomy was closed, the left kidney was removed, and the ureter was employed to create a Mitrofanoff neourethra. He subsequently underwent native nephrectomy and renal transplantation. His bladder function progressively normalized, intermittent catheterization was discontinued, and his Mitrofanoff neourethra was removed. This pathophysiology is operative to some extent in a significant percentage of pediatric ESRD patients.

In addition to maintaining as much native renal function as possible, modern bladder management has the potential to delay the need for dialysis and transplantation. This delay may significantly improve the success of both of these treatment modalities. It is imperative from the inception of urologic care that management be tailored to minimize any potential detrimental influence on subsequent dialysis and transplantation.

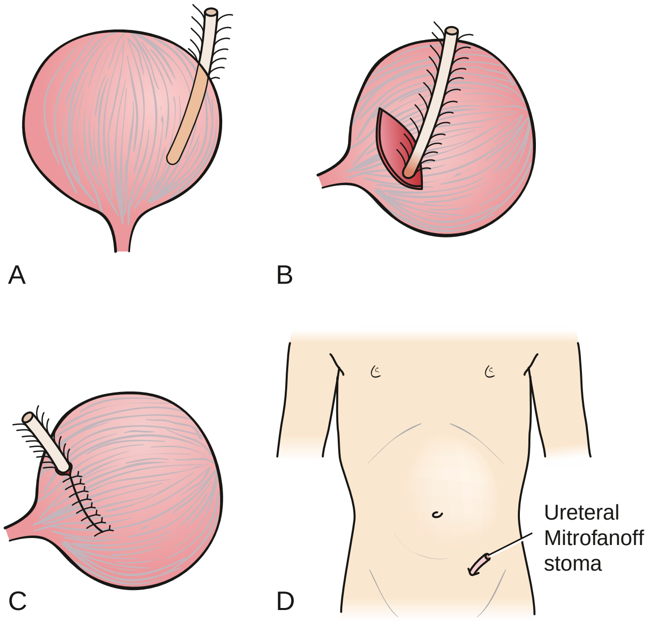

Figure 47-6 Retroperitoneal creation of a ureteral Mitrofanoff conduit. **A,** Ureter is mobilized with preservation of the adjacent vascular supply. Nephrectomy is performed (dorsal lumbotomy or flank incision). **B,** Detrusor incision is made, and a mucosal trough is developed. **C,** Detrusor flaps are approximated over the ureter. **D,** Final position of the Mitrofanoff stoma does not interfere with subsequent transplantation.

A key element in surgical care is preservation of the peritoneal cavity to allow effective peritoneal dialysis. An effort should be made to avoid transperitoneal surgery, which may prevent effective exchange of dialysate secondary to adhesions. In some instances, serosal changes can prevent effective ultrafiltration and obviate peritoneal dialysis even in the face of what would seem to be adequate volume exchanges. Consequently, an attempt is made to stabilize the urinary tract through pharmacotherapy, intermittent catheterization, and, if necessary, extraperitoneal surgery.

In selected circumstances, bladder augmentation in the form of autoaugmentation or ureterocystoplasty can be performed extraperitoneally, as can the creation of a ureteral Mitrofanoff neourethra (Fig. 47-6). These options should always be considered. If transperitoneal reconstruction is required before transplantation, this should be done when the patient is otherwise ready for wait-listing or 6 to 12 weeks before scheduled living donor transplantation.[47] The patient is maintained on hemodialysis in the interval. In exceptional instances, in which sufficient recoverable renal function seems to be present to defer dialysis, medical management fails, and extraperitoneal reconstructive options are unavailable, extraperitoneal urinary diversion (e.g., cutaneous ureterostomy or cutaneous pyelostomy) should be strongly considered. Additionally, nephrectomy can readily be performed extraperitoneally through a flank or dorsal lumbotomy approach when indicated. The extent of surgical rehabilitation feasible before transplantation is exemplified in Figure 47-7.

Another important consideration regarding augmentation relates to solute transfer and acid-base abnormalities. The metabolic effects of augmentation have been previously reviewed in detail.[11] These effects may be particularly problematic in ESRD when the kidneys are incapable of compensating for solute absorption or loss across the augmenting segment. The resultant abnormalities include acidosis and bone demineralization (small bowel and colon) and, rarely, alkalosis (stomach). In an anephric or diverted child, metabolic complications of augmentation are minimized because there is no interface between urine and the intestinal mucosa. When transplantation is performed, allograft function is generally sufficient to enable compensation, preventing significant acidosis. If allograft injury ensues, however, the risk of acidosis returns.

Gastrocystoplasty in large part obviates these metabolic complications.[48,49] With the rare exception of alkalosis, no metabolic complications are generally encountered. There is, however, a risk of hematuria-dysuria secondary to acid secretion in the urine. This symptom complex is exacerbated by oliguria and by an incompetent bladder neck because the urethra is most vulnerable to the effects of aciduria. Consequently, bladder neck competence should be ensured whenever gastrocystoplasty is performed. Hematuria-dysuria is most likely encountered during an oliguric or anuric period preceding transplantation. It is prevented or minimized by preserving native kidney urine production and by preemptive bladder irrigation, histamine receptor blockage, or proton-pump inhibition. Not only does gastrocystoplasty obviate the risk of acidosis, but it also may significantly improve the preexisting acidosis associated with ESRD itself (Fig. 47-8).[49] Other advantages of gastrocystoplasty include lower risk of UTIs and bladder stone formation than with enterocystoplasty.[50]

In addition to complicating dialysis management, urologic intervention may have an adverse effect on subsequent transplantation care. An infant with ESRD may require a transabdominal transplantation approach. Previous intra-abdominal surgery increases the risk of adhesions, which may enhance the risk of enterotomy, a particularly devastating complication in a patient receiving high-dose immunosuppression. The type of augmentation may influence the success of implantation of the allograft ureter. Native bladder is the best receptacle for the allograft ureter, followed by the stomach and the tinea of the colon. Small bowel and ureter are problematic from this perspective. Although the ureter is an ideal ESRD augmentation substrate because it is metabolically inert and can be prepared extraperitoneally, in cases in which the native bladder is excessively diseased and contracted, gastrocystoplasty becomes an important alternative (see Fig. 47-8).

Another consideration is the placement of urologic stomas and incisions. The transplantation incision may result in sacrifice of the inferior epigastric vessels. If this incision has been performed bilaterally, and previous ligation of the superior epigastric vessels has been accomplished, compromised healing or even abdominal wall necrosis may be encountered. Transverse upper abdominal incisions (e.g., for bilateral native nephrectomy) should be avoided. Of additional concern is the risk of exposure of the recipient to HLA and cytomegalovirus and other viral agents if transfusion is required. Meticulous hemostasis to reduce the need for transfusion is important. Preoperative maximization of the red blood cell volume with erythropoietin is helpful. If transfusion is required, autologous blood is an excellent option. Otherwise, cytomegalovirus-negative blood, filtered to remove leukocytes, is beneficial.

MANAGEMENT AND TRANSPLANT PREPARATION OF CHILDREN WITH CHRONIC KIDNEY DISEASE

Medical Aspects

The preparation of children for kidney transplantation is generally a multidisciplinary task shared by the patient's nephrology care team (e.g., nurses, dietitians, social workers, and nephrologists) in conjunction with other services as needed

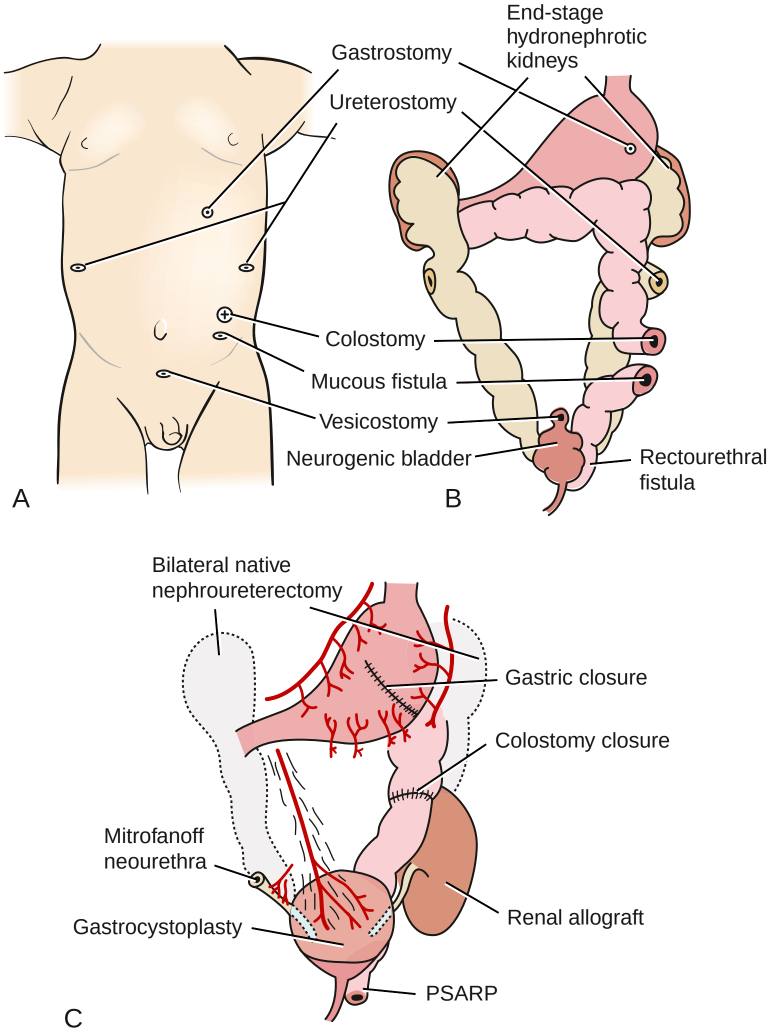
Gastrostomy
End-stage hydronephrotic kidneys
Ureterostomy
Colostomy
Mucous fistula
Vesicostomy
Neurogenic bladder
Rectourethral fistula
A
B
Bilateral native nephroureterectomy
Gastric closure
Colostomy closure
Mitrofanoff neourethra
Gastrocystoplasty
Renal allograft
PSARP
C

Figure 47-7 Urinary reconstruction and renal transplantation in a patient with the VATER association (*v*ertebral defects, imperforate *a*nus, *t*racheo*e*sophageal fistula, and *r*adial and renal dysplasia). **A,** Appearance on referral with gastrostomy, bilateral ureterostomies, colostomy, mucous fistula, and vesicostomy. **B,** Preoperative urinary and colonic status with massive hydronephrosis and small, contracted bladder. **C,** Postreconstructive status after posterior sagittal anorectoplasty (PSARP), gastrocystoplasty, creation of Mitrofanoff neourethra, bilateral nephrectomy, colostomy closure, and living donor transplantation. (From Sheldon CA. Imperforate anus, urogenital sinus and cloaca. In: King LR, Belman AB, Kramer SA, eds. *Clinical Paediatric Urology*. 4th ed. Oxford, England: Isis Medical Mediam; 2002.)

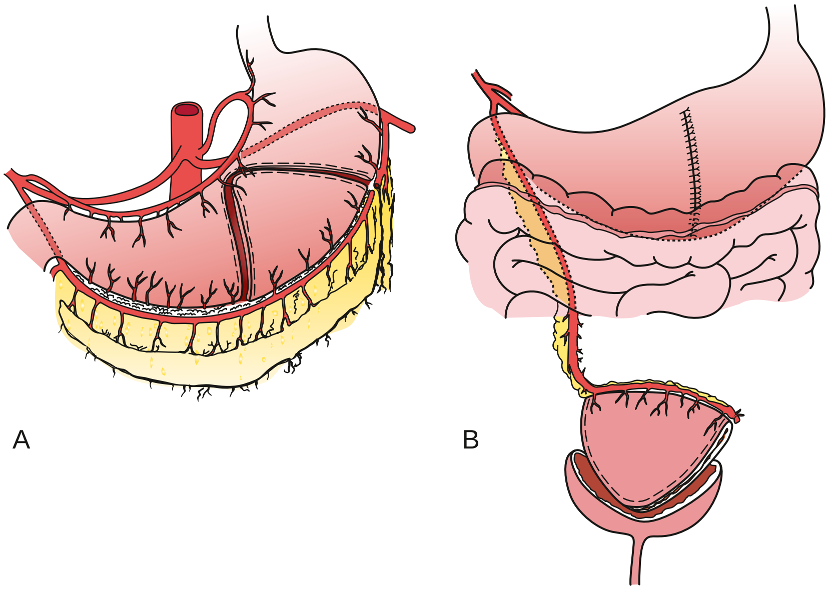

Figure 47-8 Gastrocystoplasty. **A,** Development of a right gastroepiploic pedicle and isolation of a wedge of gastric fundus. **B,** Mobilization of the right gastroepiploic pedicle through the retroperitoneal plane into the augmentation position. The stomach is closed, and the gastric segment is sutured to the widely incised native bladder. (Adapted from Mitchell ME. Gastrocystoplasty and bladder replacement with stomach. In: Marshall FF, ed. *Operative Urology*. Philadelphia: Saunders; 1991:254-255.)

(e.g., pediatric urology, surgery, psychiatry, anesthesiology, and critical care medicine). The nephrologic care of children with CKD often includes antihypertensive and antiproteinuric therapy in an attempt to delay progression to ESRD and to contain the cumulative cardiovascular morbidity created by CKD and later ESRD.[31,32] It cannot be emphasized enough how important it is to enable patients to enter the transplant procedure in the most optimal medical condition possible.

Specifically, children, similar to adults, with CKD or ESRD should be encouraged to achieve and maintain physical fitness and weight control. Cardiovascular fitness and absence of obesity reduce surgical and anesthesiologic risks associated with the transplant operation, and provide an advantage in the efforts to combat the increased risks for cardiovascular morbidity and excessive weight gain after transplantation.[51] Because transplanted children, especially when they are of school age, do not uniformly display catch-up growth (see Fig. 47-1), aggressive nutritional support is often required. Also, as indicated, rhGH therapy needs to be considered before, and possibly after, transplantation.[52] Appropriate nutritional management before transplantation, frequently paired with the prescription of phosphate binders and active vitamin D and with regular monitoring of serum parathyroid hormone levels, also attenuates post-transplant bone disease, and increases the likelihood of appropriate growth.[30,53] Before transplantation, the recipients' up-to-date immunization status needs to be ascertained because no live vaccines can be given after transplantation, and the response to other vaccines in the setting of immunosuppression may be inadequate.[54] Immunosuppressive therapy can lead to bothersome exacerbations of warts, and potential recipients should have any warts treated as definitively as possible before transplantation.

In addition to these general principles, numerous issues need to be considered on an individual basis during preparation of the recipient. Psychosocial stability of the patient and the family is of tremendous importance for adherence to the complex treatment regimen required for good long-term results.[55] Psychosocial stability is largely defined individually for each patient/family unit, and requires case-by-case interventions ranging from counseling over more intense psychological interventions to the involvement of authorities dealing with complicated custodial situations. Before transplantation, patients and families also need to be educated about the need for frequent and comprehensive follow-up, especially during the first few months after hospital discharge. This need can create significant logistical obstacles with regards to transportation and caregivers' time away from work, and many families would benefit from support in planning for this challenging period ahead of time. As part of this planning effort, it should also be ensured that the patients have appropriate coverage for their post-transplant medications, and especially that they or their caregivers know how to obtain the required immunosuppressive drugs in the outpatient setting.

Depending on the recipient's developmental and pretransplant medical (e.g., dialysis) status, plans also are necessary regarding vascular and gastrointestinal tract access. A central line may be needed for a prolonged time after transplantation to facilitate frequent blood sampling in very young recipients, recipients with very limited peripheral venipuncture sites, and recipients who may need pretransplant and post-transplant plasmapheresis for immunologic reasons (see later) or because they are considered to be at high risk for recurrence of focal segmental glomerulosclerosis.[56] A gastrostomy tube is essential in patients who require supplementation of additional nutrition or fluid or are unable to take all their post-transplant medications by mouth. Lastly, a subgroup of patients is at increased immunologic risk from a previous kidney or other organ transplant, from blood transfusions, or from other sensitizing events. These individuals benefit from specialized immunologic characterization and consequently from consideration of desensitization strategies before transplantation to enhance their potential for graft acceptance and long-term graft survival.[57-59]

Before actual transplantation, a risk assessment of the recipient for thrombotic complications is important because graft thrombosis is a significant cause of pediatric transplant loss.[60,61] Risk factors include hypercoagulopathy (e.g., as seen in chronic nephrotic states), antiphospholipid antibodies (seen in 30% to 50% of patients with systemic lupus erythematosus), prior thrombosis of a large vein postoperatively (e.g., a renal transplant vein), and thrombosis associated with vascular access (e.g., for dialysis).[62] Hypercoagulability should be corrected before the transplant procedure whenever possible. Alternatively, prescription of anticoagulation during and after the transplant should be considered, although controversy exists regarding the routine use of heparin in the perioperative period to reduce the incidence of renal allograft thrombosis. A more recent retrospective study showed that young recipient age, young donor age, and increased cold ischemia time were associated with a higher risk for graft thrombosis, but the administration of heparin did not decrease the incidence of early renal allograft thrombosis.[63]

Urologic Aspects

As outlined in Figure 47-9, the transplantation process is almost overwhelmingly complex and potentially error-prone. In addition to care provided by the transplantation surgeon and the nephrologist, the process is heavily influenced by the involvement of primary care physicians and urologic surgeons, and by the organ procurement agency and laboratory personnel. The transplantation physician may be placed at a tremendous disadvantage as a consequence of previous suboptimal recipient care or as a result of problems created by physicians caring for the donor before death and organ procurement surgeons and registry or laboratory personnel. When complications are averted or managed successfully, however, good long-term patient and allograft survival are achievable (see later).

In some instances, a preemptive, as opposed to interventional, approach may be considered. The advantages to preemptive transplantation, in which the patient receives a transplant before the institution of dialysis, are the avoidance of the morbidity and psychological impact of profound renal insufficiency, dialysis access surgery, and dialysis itself. Although the concern that avoidance of the dialysis experience may adversely affect the child's motivation to care for the allograft has been raised in the past, more recent NAPRTCS data show a significant allograft survival advantage with preemptive transplantation.[64] There are probably several reasons for the better outcomes of preemptive kidney transplantation compared with transplantation after initiation of long-term dialysis.[65]

When accepted as a transplantation candidate, the recipient undergoes careful preparation. The critical concerns regarding the maximization of growth; nutrition; red blood cell mass; acid-base, electrolyte, cardiovascular, and volume parameters; and immunization status[66] have been previously discussed. Optimization of the urinary tract, which serves as the receptacle for the future allograft, is equally important. Table 47-4 outlines the basic evaluation of the recipient; Figure 47-10 depicts the pretransplantation recipient evaluation from a urologic perspective. Basic to this process is the understanding that the adverse effect of a dysfunctional bladder on an allograft can be overwhelming, that surgical correction

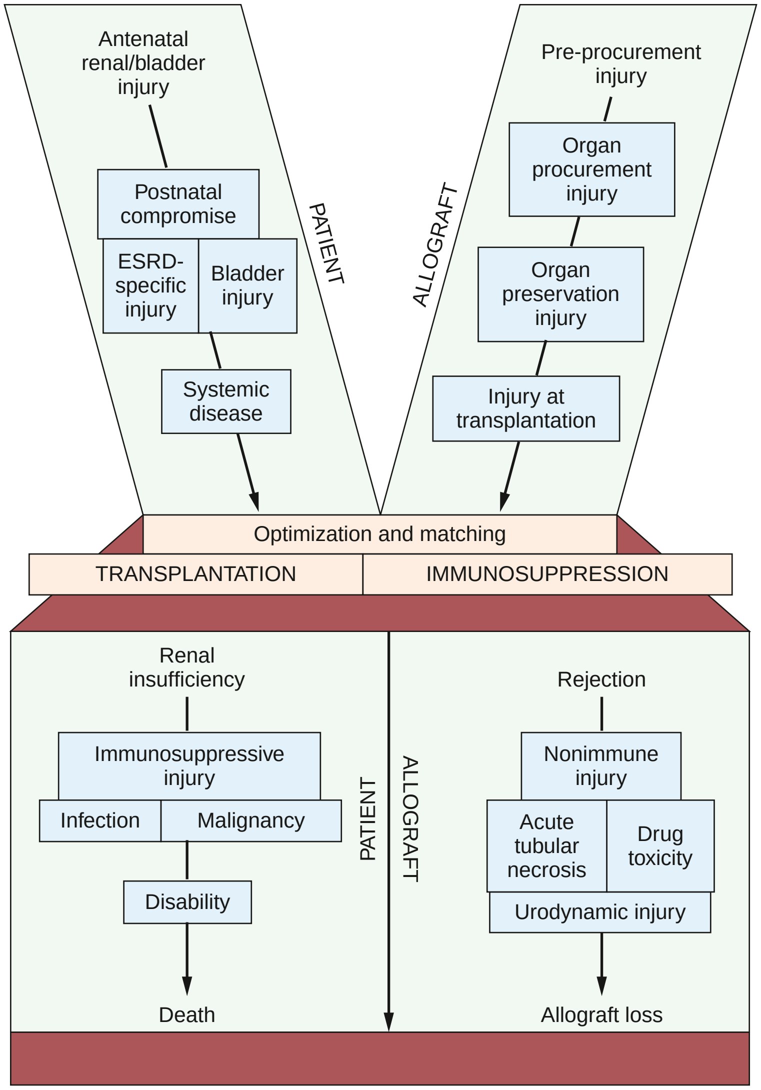
Antenatal renal/bladder injury
Postnatal compromise
ESRD-specific injury
Bladder injury
Systemic disease
PATIENT
ALLOGRAFT
Pre-procurement injury
Organ procurement injury
Organ preservation injury
Injury at transplantation
Optimization and matching
TRANSPLANTATION
IMMUNOSUPPRESSION
Renal insufficiency
Immunosuppressive injury
Infection
Malignancy
Disability
Death
PATIENT
ALLOGRAFT
Rejection
Nonimmune injury
Acute tubular necrosis
Drug toxicity
Urodynamic injury
Allograft loss

Figure 47-9 Patient and allograft perspectives regarding potential problems encountered in the transplantation process (see text for details). ESRD, end-stage renal disease.

of identified abnormalities is most safely applied before immunosuppression, and that transplantation is only rarely sufficiently urgent to preclude formal urologic evaluation and preparation, even if this means some time on long-term dialysis for the recipient.

All pediatric transplantation candidates undergo a urologic history and physical examination. An inferred urologic cause of renal injury, a history of UTI, obstructive or irritative voiding symptoms during the preoliguric or prepolyuric phase of renal insufficiency, and an abnormal neurologic or sacral examination are specific indications for aggressive evaluation with radiographic voiding cystourethrography and formal urodynamic testing. All children undergo urine culture testing, and PVR measurement and renal-bladder ultrasound screening. Children too young during the normovolemic period of urine output to assess voiding symptoms or who have hydronephrosis or bladder wall thickening or irregularity on renal-bladder ultrasound undergo screening radiographic voiding cystourethrography. Similarly, the presence of reflux and detrusor or bladder outlet distortion on radiographic voiding cystourethrography is an indication for formal urodynamic testing.

Formal urodynamic testing should include uroflowmetry and sphincteric electromyography to assess for dyssynergy, occult intermittency, or straining to void. Cystometrography determines the effective compliance (capacity <40 cm H_2O), the presence of uninhibited detrusor activity, and the leak point and stress leak point pressures, which reflect continence potential. Care should be taken not to overinterpret a diminished bladder capacity in patients with oliguric renal failure or urinary diversion. Unexplained functional or structural bladder abnormalities may require cystourethroscopy. Patients who have renal insufficiency secondary to a primary nephrologic disorder and who, during their normovolemic voiding phase, were free of voiding symptoms or infection require neither radiographic voiding cystourethrography nor formal urodynamic testing.

If a significant symptom complex or urodynamic abnormality is encountered, an attempt is made to control the bladder with a voiding regimen, anticholinergic therapy, or intermittent catheterization. Because dysfunctional defecation can adversely affect voiding, and because obstipation and fecal incontinence (when present) are best managed before transplantation, an aggressive bowel program may

Table 47-4 Basic Evaluation of the Renal Transplant Recipient

- History and physical examination
  - Immunization status
  - General history and physical examination
  - Serial height, weight, and head circumference measurement
  - Serial blood pressure measurement
  - 24-hr urine output measurement
  - Stool guaiac test
- Immunologic tests
  - HLA-A, HLA-B, and HLA-C typing
  - HLA-DR typing
  - Interval screening
  - Lymphocytotoxic antibodies, and donor-specific/anti-HLA antibodies as indicated
  - Storage for crossmatching
  - Fluorescent antinuclear antibodies, antistreptolysin O, anti–glomerular basement membrane antibodies
- Blood bank tests
  - ABO and Rh typing
  - Crossmatching
- Microbiologic tests
  - Urine culture
  - Rapid plasma reagin test
  - Mantoux test
- Virology titers
  - Cytomegalovirus
  - Herpes simplex virus
  - Varicella-zoster virus
  - Epstein-Barr virus
  - Hepatitis B and C profiles
  - HIV test
- Laboratory tests
  - Complete blood cell count with differential
  - Prothrombin time, partial thromboplastin time, and thrombin time
  - Urine protein levels (24-hr urine protein as indicated)
  - Blood urea nitrogen, creatinine, electrolyte, calcium, magnesium, phosphorus levels
  - Liver function studies
  - Serum protein profile as indicated
  - Uric acid
- Radiologic examination
  - Renal ultrasonography
  - Hand and wrist, skull, and clavicle films
- Special (individualized) tests
  - Chest radiography
  - Electrocardiogram and ophthalmologic examination (hypertension, diabetes)
  - Dental evaluation and sinus films
  - Review of renal pathology specimens
  - Psychology consultation (compliance concerns)
  - Voiding cystourethrography, cystourethroscopy (see text)
  - Esophagogastroduodenoscopy

HIV, human immunodeficiency virus; Rh, rhesus factor.

Modified from Sheldon CA, Martin LW, Churchill BM. Surgical perspectives in pediatric renal transplantation. In: Gillenwater JY, Grayhak JT, Howards SS, et al, eds. *Adult and Pediatric Urology.* Chicago: Year Book Medical; 1987:2086.

be indicated as well. Commonly, voiding is not evaluable because of urinary diversion or oliguria. In such instances, pretransplantation urinary undiversion can be an invaluable tool to help ensure adequate bladder function and can be done without significant risk of precipitating premature dialysis.[67] Rarely, a structurally or urodynamically unsound bladder cannot be adequately addressed because of oliguria. In this situation, bladder cycling via intermittent catheterization may help ensure candidacy.

If a continent, compliant, sterile, and evacuatable urinary tract cannot be ensured with this process, surgical reconstruction is indicated. Table 47-5 outlines the indications for pretransplantation nephrectomy.[11,68-71] In addition to the traditional indications common to children and adults, congenital nephrotic syndrome has emerged as an important indication for pretransplantation nephrectomy[70,71] because of a definable increased risk of vascular graft thrombosis and an apparent increase in septic death.[71,72] Acquired renal cystic disease is a well-recognized entity in adults with ESRD with a definable natural history. This entity is less well appreciated in children but definitely occurs at a significant incidence.[73] Malignant degeneration in the pediatric age range also is reported.[73] Because of the unknown natural history and the long life expectancy of a child with ESRD, nephrectomy should be strongly considered until more data are generated.

Several strategic considerations regarding nephrectomy are relevant. While the patient is awaiting transplantation, the presence of a significant urinary volume may substantially contribute to the effectiveness of peritoneal dialysis and hemodialysis. Consequently, if only one kidney requires removal, this can be done at the time of transplantation and often through the same incision as the transplantation itself. If two kidneys require removal, a differential function analysis by isotope imaging is performed, and the worse kidney is removed. The second kidney is removed at the time of transplantation. Exceptions to this approach include the presence of renal-mediated intractable infection or hypertension and the presence of massively enlarged (e.g., polycystic) or significantly surgically altered kidneys (e.g., diversion), which may make nephrectomy at the time of transplantation unduly difficult or complicated. As previously addressed, the nephrectomy incision should be positioned so as not to interfere with subsequent transplantation.

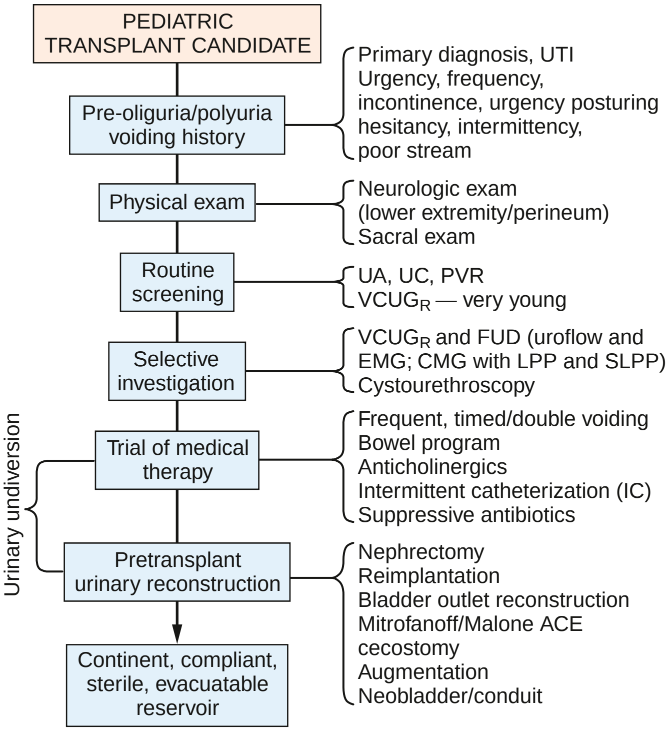
PEDIATRIC TRANSPLANT CANDIDATE
Pre-oliguria/polyuria voiding history
Primary diagnosis, UTI
Urgency, frequency, incontinence, urgency posturing
hesitancy, intermittency, poor stream
Physical exam
Neurologic exam (lower extremity/perineum)
Sacral exam
Routine screening
UA, UC, PVR
VCUG_R — very young
Selective investigation
VCUG_R and FUD (uroflow and EMG; CMG with LPP and SLPP)
Cystourethroscopy
Trial of medical therapy
Frequent, timed/double voiding
Bowel program
Anticholinergics
Intermittent catheterization (IC)
Suppressive antibiotics
Urinary undiversion
Pretransplant urinary reconstruction
Nephrectomy
Reimplantation
Bladder outlet reconstruction
Mitrofanoff/Malone ACE cecostomy
Augmentation
Neobladder/conduit
Continent, compliant, sterile, evacuatable reservoir

Figure 47-10 Pretransplantation urologic evaluation (see text). ACE, antegrade continence enema; CMG, cystometrography; EMG, electromyography; FUD, formal urodynamic testing; LPP, leak point pressure; PVR, postvoid residual; SLPP, stress leak point pressure; UA, urinalysis; UC, urine culture; VCUG_R, radiographic voiding cystourethrography.

Table 47-5 Indications for Pretransplantation Native Nephrectomy

Chronic renal parenchymal infection
Infected urolithiasis
Heavy proteinuria*
Intractable hypertension
Polycystic disease†
Acquired renal cystic disease‡
Infected reflux§
Infected hydronephrosis

*Particularly congenital nephrotic syndrome, which may be associated with hypercoagulable states and increase the risk of death from infection.

†Massive dimension compromising respiration, gastrointestinal function, or allograft placement; infection; bleeding.

‡In adults, when adenocarcinoma is suspected. In children, an unknown natural history and a long lifetime risk of exposure may favor nephrectomy in all instances.

§Often manageable by ureteral reimplantation, allowing preservation of native renal function and ureter that might be subsequently needed for reconstruction.

Modified from Ramos E, Kasiske B, Danovitch G. Pre-transplant evaluation of the recipient. In: Norman DL, Suki WN, eds. *Primer on Transplantation.* Thorofare, NJ: American Society of Transplant Surgeons; 1998:175.

The fate of the retained native renal unit with VUR is incompletely understood, and management is controversial. An increased incidence of acute symptomatic UTI in patients with continued native ureteral reflux has been shown compared with controls and with patients with previously corrected reflux,[74,75] although other studies have not confirmed this tendency.[76] The consensus is that VUR associated with persistent or recurrent infection should be managed by ureteral reimplantation or nephroureterectomy. Whenever possible, ureteral reimplantation is preferable to preserve the native ureter, facilitating the management of any future allograft ureteral complication that might arise. Additionally, higher grade, dilating VUR is associated with sufficient morbidity to justify pretransplantation ureteral reimplantation.[55] Additional considerations may be operative. Patients with a dysfunctional bladder associated with persisting or recurring bacteriuria (symptomatic or asymptomatic) or intermittent catheterization may benefit from ureteral reimplantation even in the presence of nondilating VUR.

Surgical reconstruction to enable continence may be required for a patient with neurologic (e.g., the VACTERL association [*v*ertebral defects, imperforate *a*nus, *c*ardiac anomalies, *t*racheo*e*sophageal fistula, *r*adial and renal dysplasia, and *l*imb anomalies]) or structural (e.g., cloacal exstrophy) impairment of the urinary bladder. This reconstruction is best accomplished before transplantation, and the surgical strategy has been extensively reviewed.[11] Bladder outlet reconstruction and the surgical establishment of a continent and easily catheterizable Mitrofanoff stoma are particularly successful and beneficial when indicated. Additionally, refractory fecal incontinence should be addressed. Similar to the Mitrofanoff neourethra, the Malone continent cecostomy for the purpose of antegrade continence enema has proved safe and effective in ESRD and renal transplantation.

Bladder augmentation procedures occasionally may be necessary before transplantation to ensure continence and a urinary receptacle that operates at a sufficiently low pressure to avoid allograft deterioration. As discussed earlier, strong evidence exists documenting a relationship between high intravesical pressures and renal deterioration. Renal allograft deterioration with graft loss, azotemia, or infection has been shown in systems known to be associated with high intravesical pressures (e.g., posterior urethral valves).[42,43,77-80] That this association is not simply a consequence of an irregular reservoir with inconsistent emptying is evidenced by the excellent experience with transplantation into abnormal urinary bladders not associated with elevated intravesical pressures (e.g., prune-belly syndrome).[44] Several series report excellent outcomes, however, with transplantation into the nonsurgically altered posterior urethral valve bladder.[81-86] This seemingly conflicting experience is readily explained by the large variability in the urodynamic characteristics of the valve bladder, the small number of patients reported in individual series, and the tendency for valve bladder function to mature and improve with age as discussed earlier.

Nonetheless, these experiences have created much controversy about augmentation in the transplantation setting. Bladder augmentation is capable of complicating the course of a recipient and should be applied only when a definitive indication is shown.[87] A bladder defunctionalized because of severe oliguria or previous diversion may appear contracted and urodynamically unsound only to expand with cycling and provide a hospitable reservoir. Generally, bladders defunctionalized because of severe oliguria subsequent to primary renal disease are not problematic and do not require urodynamic investigation even if the capacity is found to be low. In contrast, bladders defunctionalized by diversion to interrupt ongoing native renal injury owing to high intravesical pressures must be highly suspect. In the case of posterior urethral valves, a noncompliant, threatening bladder documented early in life may not be so when transplantation is performed at an older age. Interpretation of urodynamic findings and the choice of augmentation cystoplasty must be highly individualized. That failure to apply augmentation can adversely affect the clinical course of the recipient is clearly shown by numerous reported augmentations required after transplantation because of renal deterioration.

Figure 47-11 reviews the available literature on bladder augmentation in the transplant recipient.[11,88-96] Most patients are 6 to 20 years old, and the most common primary diagnosis is posterior urethral valves, followed by neurovesical dysfunction. Although ileocystoplasty is the most prevalent procedure, several modalities have been successfully employed. Most patients (59%) received living related donor allografts. Grafts from deceased donors have been used, however, with comparable success. At the time of reporting, 80% of allografts were functioning well, whereas in 18% allograft function had been lost, and in 2% the recipient had died with a functioning graft. Each instance of allograft loss was due to chronic rejection, with no graft loss reported from infectious or technical complication.

Table 47-6 compares the available types of augmentation procedures in relation to their applicability to the transplantation setting. Augmentation is best avoided whenever it is safe to do so. Autoaugmentation and ureterocystoplasty can be performed extraperitoneally without interfering with peritoneal dialysis or intestinal function, and without a risk of metabolic consequences. The clinical experience is quite limited, however, and the applicability is low. Seromuscular augmentation also is free of metabolic consequence. The clinical experience and applicability seem to be low, and the procedure is relatively complex.

Ileocystoplasty and colocystoplasty are technically simple procedures that have been used extensively with good result. They risk the development of profound acidosis, however. Although ureteral or Mitrofanoff neourethral implantation can be successfully performed into the tinea of the colonic augmentation segment, reliable implantation is impossible with ileocystoplasty, a feature shared by autoaugmentation and ureterocystoplasty. Ileocystoplasty and colocystoplasty are associated with an increased incidence of bacteriuria, and the resultant mucus production may compromise catheter drainage. The risk of bladder calculi is also significantly increased. Gastrocystoplasty has proved highly applicable to the transplantation setting, avoids the risk of acidosis and calculi, and markedly reduces the incidence of significant bacteriuria and mucus production. Ureteral and Mitrofanoff neourethral implantation are readily performed. The hematuria-dysuria complex is occasionally encountered, particularly during highly oliguric or anuric periods while the patient awaits transplantation. It is generally readily controlled by bladder cycling, histamine blockade, or proton-pump inhibition.

Whenever possible, allograft ureteral implantation should be accomplished into the native component of the augmented bladder[97] or into a gastrocystoplasty segment to reduce the risk of ureteral complications. If a nonreconstructable bladder is encountered, an intestinal conduit or continent diversion may be applicable.[98] The risks of technical and infectious complications are sufficiently high, however, to obviate their use unless native bladder rehabilitation is impossible.[97,99] An isotopic neourethra and bladder, when applicable, provide an excellent alternative (Fig. 47-12).[100]

OBTAINING A DONOR KIDNEY

According to more recent Organ Procurement and Transplantation Network data, approximately 20 children (3%) wait-listed to receive a deceased donor kidney die each year (www.optn.org, February 2007). Efforts are ongoing to optimize organ donation rates from deceased donors and to refine organ selection criteria for children. A useful rule of thumb is that the best kidney for a child is one from an otherwise healthy teenage or young adult donor, and that a single kidney from a very young pediatric donor would not provide acceptable long-term function.[101] Under selected circumstances, however, consideration can be given to the transplantation of an en bloc pair of kidneys from a very young donor into a pediatric recipient.[102] Similarly, the use of kidneys from deceased donors meeting expanded criteria or even from non–heart-beating donors, which is gaining increasing ground in adult kidney transplantation, is currently indicated only for children in extremely rare situations because these organs are unlikely to provide the very long graft survival desired especially for pediatric recipients. Generally, individuals who are being evaluated as potential deceased donors have experienced brain death.

The sequence of steps and diagnostic studies involved in this evaluation, including contraindications to the use of organs from a deceased donor, has been thoroughly reviewed.[103-105] Table 47-7 outlines the general evaluation of deceased kidney donors. Donor management requires intensive and coordinated care on the part of the intensive care unit and organ procurement team members.[103] Hemodynamic stabilization is crucial and generally involves central venous or pulmonary arterial pressure monitoring, volume and red blood cell mass expansion, replacement of coagulation components (for disseminated intravascular coagulation), correction of dysrhythmias, and judicial use of vasopressors. Temperature regulation and respiratory support are also crucial and often problematic. Hormonal support is often indicated because of a precipitous decrease in hormone levels after the onset of brain death and may include triiodothyronine, cortisol, and insulin. Arginine vasopressin is frequently indicated to reverse the often-encountered severe neurogenic diabetes insipidus.[103-105]

Surgical organ retrieval is performed through a midline incision extending from the sternal notch to the pubis.[103,104] The intestines are mobilized, and the distal aorta and inferior vena cava are isolated. As necessary, the vascular anatomy of the liver, pancreas, and small intestine is defined, and the aorta is isolated at the level of its diaphragmatic hiatus. The

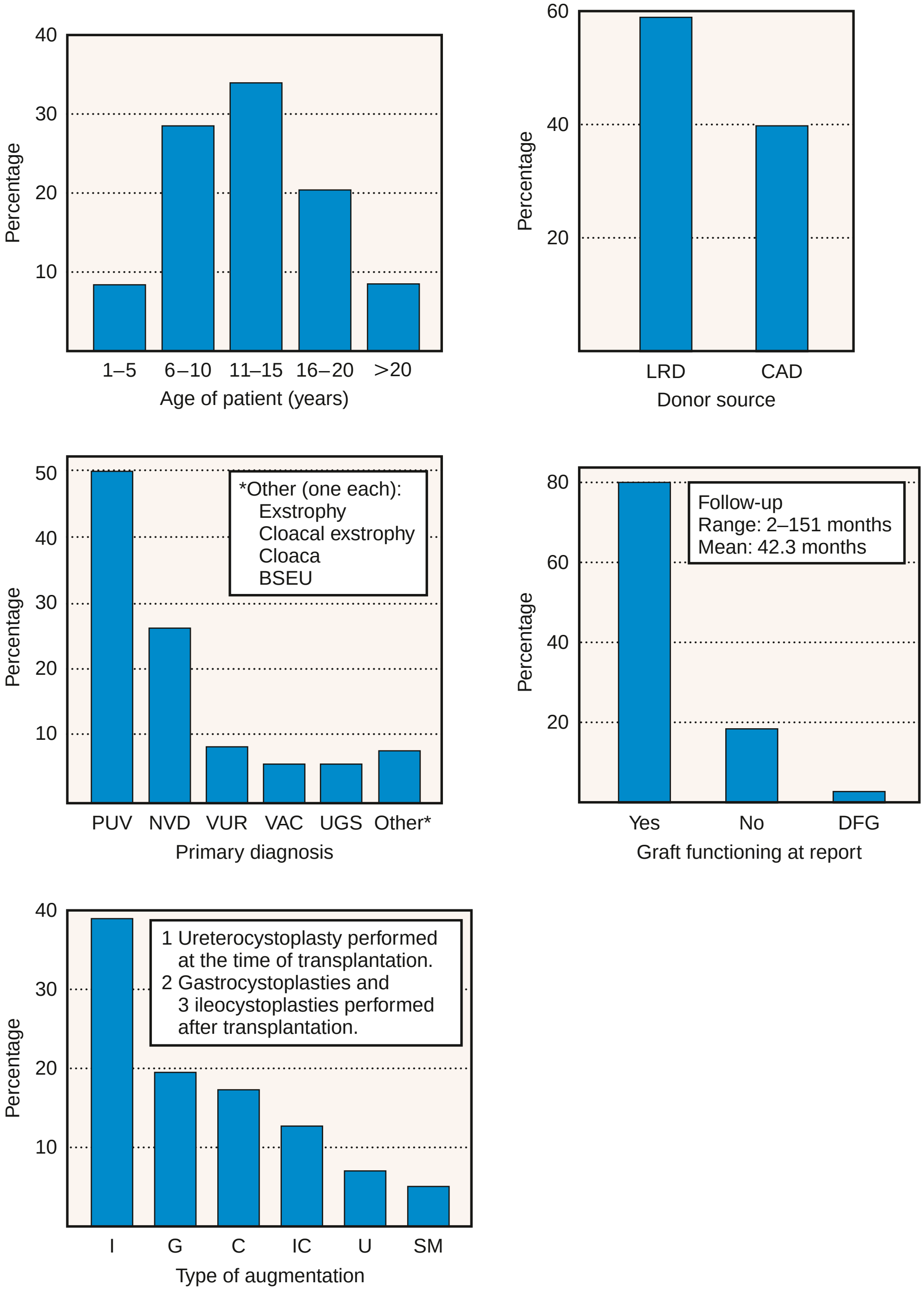

Figure 47-11 Transplantation into the augmented bladder: summary of reported clinical experience. BSEU, bilateral single ectopic ureters; C, colocystoplasty; CAD, cadaveric donor; DFG, death with functioning graft; G, gastrocystoplasty; I, ileocystoplasty; IC, ileocecocystoplasty; LRD, living related donor; NVD, neurovesical dysfunction; PUV, posterior urethral valves; SM, seromuscular colocystoplasty; U, ureterocystoplasty; UGS, urogenital sinus; VAC, VACTERL association (*v*ertebral defects, imperforate *a*nus, *c*ardiac anomalies, *t*racheo*e*sophageal fistula, *r*adial and renal dysplasia, and *l*imb anomalies); VUR, vesicoureteral reflux.

distal aorta is cannulated, the supraceliac aorta is clamped, venous drainage is achieved (generally at the level of the right atrium), the aorta is flushed with cold preservation solution, and the abdomen is packed with sterile saline ice slush. Organs are sequentially removed, beginning with the heart, followed by the lungs, liver, small intestine, or pancreas, and, finally, the kidneys. The kidneys are removed en bloc with the adjacent aorta and vena cava, and the ureters are divided at the level of the urinary bladder. Kidneys from a very young donor are not separated until a decision has been made about whether or not they will be transplanted individually or en bloc. Otherwise, the kidneys are separated on the back table and cold stored for distribution.

The preservation fluid constituents are designed to minimize the injury associated with hypothermia and hypoxia, and represent some of the most pivotal work in transplantation science. The principal active ingredients of the two most prevalent solutions are outlined in Table 47-8.[103,104] A significant benefit in delayed graft function and 1-year graft survival favoring University of Wisconsin solution over EuroCollins solution has been shown.[106] The osmotic swelling and sodium pump paralysis associated with hypothermia are compensated by the elimination or reduction of chloride, whose intracellular shift facilitates osmotic edema, in favor of impermeable ionic agents such as phosphate, sulfate, and lactobionate. Osmotic impermeants, such as lactobionate,

Table 47-6 Considerations in Pretransplantation Bladder Augmentation

Augmentation Type	Advantages	Disadvantages	Applications
None	Lowest risk of complication	Renal injury if bladder noncompliant	Whenever possible
Autoaugmentation	No metabolic consequences	Augmentation surface not amenable to ureteral or MNU implantation	Sufficient native bladder surface for implantation
	May be performed extraperitoneally	Risk of perforation	Near-normal bladder capacity
		Limited clinical experience	
Ureterocystoplasty	No metabolic consequences	Augmentation surface not amenable to ureteral or MNU implantation	Sufficient native bladder surface for implantation
	May be performed extraperitoneally	Requires presence of large dilated ureter	
Seromuscular augmentation	No metabolic consequences	Augmentation surface less amenable to ureteral or MNU implantation	Sufficient native bladder surface for implantation
			Near-normal bladder capacity
Ileocystoplasty	Technically simple	Augmentation surface less amenable to ureteral or MNU implantation	Sufficient native bladder surface for implantation
		Acidosis, mucus, or infection	Stomach unavailable
Colocystoplasty	Technically simple	Acidosis, mucus, or infection	Stomach unavailable
	Ureteral or MNU implantation possible		
Gastrocystoplasty	Avoids acidosis, mucus, or infection	Hematuria or dysuria	Wide application
	Ureteral or MNU implantation readily performed	Rare alkalosis	

MNU, Mitrofanoff neourethra.

raffinose, and hydroxyethyl starch, contribute further to reducing intercellular swelling. Intracellular acidosis is compensated by the avoidance of glucose and the addition of phosphate as a hydrogen ion buffer. Oxygen free radical–induced reperfusion injury is compensated by allopurinol and glutathione, and the depletion of high-energy phosphate compounds is countered by the addition of adenosine.

Although the outcomes of deceased donor kidney transplantation in children have become almost equivalent to the outcomes of living donor transplantation (Fig. 47-13), the latter remains the preferred mode of transplantation, mostly because it is easier to time. When a transplant date is set, arrangements also can be made to initiate immunosuppressive therapy ahead of time, typically several days before transplant at centers choosing this approach, to facilitate therapeutic drug levels at the actual time of surgery. Data supporting this practice as a means to improve outcome are unavailable.[107]

Living donor transplantation also makes the performance of a preemptive transplant (i.e., transplantation just before dialysis needs to be initiated) easier (see earlier). Preemptive transplantation has numerous advantages[65] and should be considered whenever possible. In the setting of preemptive transplantation, especially when an adult kidney is placed into a small child, caution with pretransplant immunosuppression (see later) should be exercised because these recipients can be quite uremic, and treatment with a calcineurin inhibitor for many days before transplantation may worsen this condition further. Under these circumstances, a grafted adult kidney that functions immediately can remove uremic toxins at a staggering rate and create a clinical scenario similar to the dysequilibrium syndrome seen in the setting of zealous, typically first-time, hemodialysis.

Living related and, increasingly, unrelated donor renal allografts have become an integral component of pediatric renal transplantation and are managed from an entirely different perspective.[108-110] Great care is required to ensure that the donor is acting on his or her own volition without coercion. Although most such allografts are obtained from direct relatives, with an obvious genetic advantage in terms of HLA matching, suitable unrelated living donors are accepted as well. Most centers require evidence of an ongoing emotional commitment (e.g., a step-parent) when entertaining unrelated directed donation, but even an unrelated, undirected donor (i.e., “Good Samaritan”) is now considered acceptable in the setting of adequate and thorough evaluation and allocation policies.

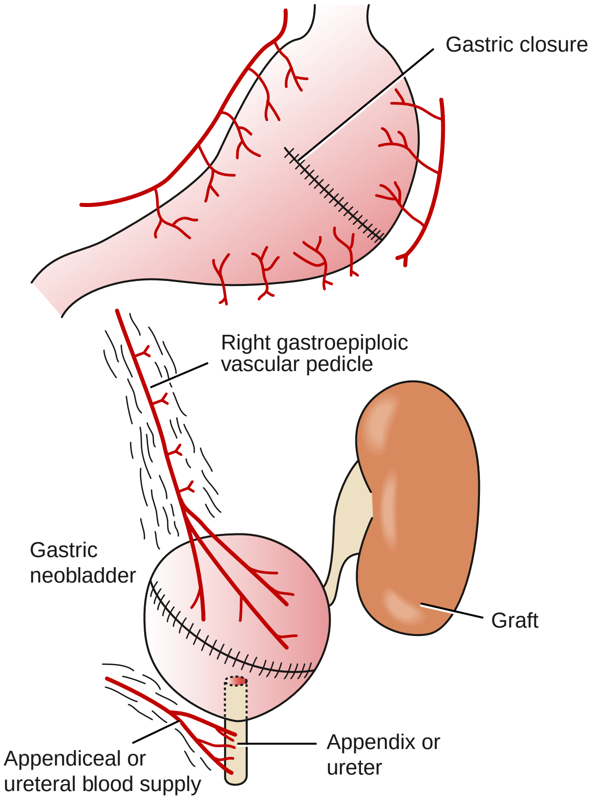
Gastric closure
Right gastroepiploic vascular pedicle
Gastric neobladder
Graft
Appendiceal or ureteral blood supply
Appendix or ureter

Figure 47-12 Total anatomic urinary replacement with renal transplantation. An isotopic neobladder is constructed from a segment of stomach or a composite of stomach and small bowel. An isotopic neourethra is constructed from appendix, ureter, or tubularized ilium and implanted into the neobladder. After a period of healing and recovery, a renal transplantation is performed with the ureter implanted into the gastric component of the neobladder. (From Sheldon CA, Welch TR. Total anatomic urinary tract replacement and renal transplantation: a surgical strategy to correct severe genitourinary anomalies. *J Pediatr Surg*. 1998;33:635.)

The long-term outcome of transplantation favors living donors (even unrelated) over well-matched grafts from deceased donors, underscoring the critical impact of minimal cold ischemia time and the absence of preharvesting renal injury or disease.[108] The virtual absence of delayed graft function, fewer episodes of rejection, and less accumulated exposure to immunosuppressant agents are other advantages that are particularly important in children because survival of the graft, level of graft function, and intensity of immunosuppression are important determinants of morbidity and mortality in this population.[111]

Generally, the morbidity associated with living related donor nephrectomy is small. Elevated systolic pressure, proteinuria, and a reduced glomerular filtration rate have been documented decades after donation.[109] Progression to significant hypertension or symptomatic renal disease after nephrectomy has proved to be rare, however.[109,112] Table 47-9 outlines the clinical evaluation and selection criteria for the proposed living renal donor. This evaluation or parts of it should be repeated as needed if the intended transplant is postponed significantly.

Donor nephrectomy is performed simultaneously with the surgical exposure of the recipient. Historically, live donor nephrectomy has been performed through an extended flank incision, which enables excellent retroperitoneal exposure of the renal hilar vessels and the ureter. In the last few years, the popularity of laparoscopic donor nephrectomy has increased

Table 47-7 Evaluation of Deceased Organ Donor Candidate

- History and physical examination
- Hematologic tests
  - Complete blood cell count, platelet count, prothrombin time, and partial thromboplastin time
- Chemistry tests
  - Electrolyte, blood urea nitrogen, creatinine, calcium, phosphate levels, urinalysis, and liver function tests
- Microbiologic tests
  - Blood, urine, and sputum cultures; sputum Gram stain; and results of prior cultures if patient febrile while hospitalized
- Serologic tests
  - Rapid plasma reagin test; tests for hepatitis B surface antigen, hepatitis C virus, HIV, cytomegalovirus, and Epstein-Barr virus; ABO and Rh typing; and HLA tissue typing
- Respiratory tests
  - Chest radiograph and arterial blood gas measurement
- Cardiovascular (heart donor)
  - Electrocardiogram and echocardiogram

HIV, human immunodeficiency virus; Rh, rhesus factor.
Modified from Ryckman FC. Organ donation, procurement and preservation. In: Oldham KT, Colombani PM, Foglia RP, eds. *Surgery of Infants and Children: Scientific Principles and Practice.* Philadelphia: Lippincott-Raven; 1997:701.

Table 47-8 Composition of Cold Storage Solutions

Substance	EuroCollins	University of Wisconsin
NA^+	9.3	
K^+	107	
Cl^-	14	
HCO_3^-	9.3	
PO_4^{2-}	93	
K^+ lactobionate		100
KH_2PO_4		25
$MgSO_4$		5
Glucose	182	
Raffinose		30
Hydroxyethyl starch (g/L)		50
Glutathione		3
Adenosine		3
Insulin (mg/L)		40
Dexamethasone (mg/L)	8	
pH	7.0	7.4
Osmolarity (mOsm/L)	325	320

Modified from Ryckman FC. Organ donation, procurement and preservation. In: Oldham KT, Colombani PM, Foglia RP, eds. *Surgery of Infants and Children: Scientific Principles and Practice.* Philadelphia: Lippincott-Raven; 1997:701.

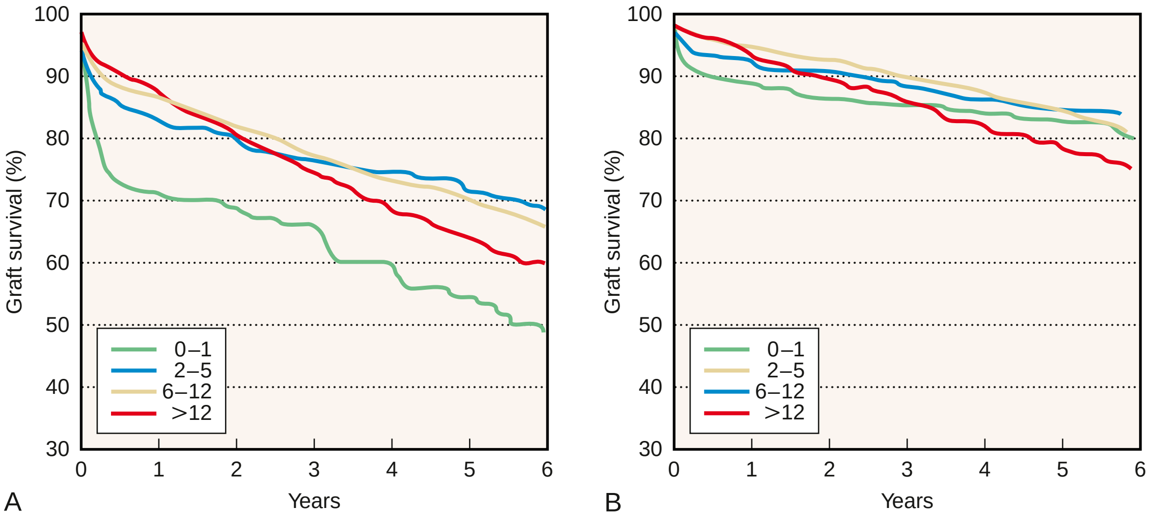

Figure 47-13 Current deceased **(A)** and living donor **(B)** 6-year graft survival rates by recipient age groups. Note the inferior early outcomes in infants receiving a transplant from a deceased donor, and the attenuated long-term success rates in teenage recipients. (From the 2006 NAPRTCS Annual Report.)

Table 47-9 Evaluation of Living Donor Candidate

Evaluation	Exclusion Criteria
Initial Screening	
Histocompatibility: ABO typing; crossmatching; tissue typing	Incompatibility; positive crossmatch
History and physical examination	Younger than legal age of consent; diabetes mellitus; obesity; hypertension; significant cardiovascular or pulmonary disease; substance abuse; malignancy (unless remote); transmissible infectious disease
Psychosocial evaluation	Evidence of coercion; not willing donor; consider "medical alibi"
Pregnancy test (women)	Positive test
Secondary Screening	
Laboratory studies: complete blood cell count; prothrombin time; partial thromboplastin time; fasting glucose level; electrolyte, liver enzyme, fasting cholesterol, calcium, phosphorus, albumin, total protein, uric acid levels	Significant uncorrectable abnormality
Renal assessment: urinalysis; serum creatinine, blood urea nitrogen levels; 24-hr creatinine clearance, protein excretion; renal ultrasonography or intravenous urography; renal arteriography (if other studies normal)	Creatinine clearance <80 mL/min/1.73 m^2; proteinuria >300 mg/24 hr; hematuria >10; 15 red blood cells/high-power field; polycystic kidney disease; urolithiasis; renal or collecting system abnormality (highly individualized)
Chest radiograph	Significant cardiac or pulmonary abnormality
Screening for infection: tests for cytomegalovirus, HIV, hepatitis B surface antigen, hepatitis C virus, Epstein-Barr virus, purified protein derivative; urine culture	HIV, hepatitis B virus, hepatitis C virus, cytomegalovirus, or Epstein-Barr virus positivity; if recipient naive may indicate use of another donor if available
Women: mammography within 1 yr if >40 yr; pelvic examination with Pap smear within 1 yr	Malignancy
Men: rectal examination; prostate-specific antigen test if >40 yr	Malignancy
Tertiary Screening	
Family history of diabetes or borderline fasting glucose level; 2-hr postprandial glucose level; glycosylated hemoglobin level; oral glucose tolerance test	Diabetes mellitus
Risk of cardiac disease (older donor, risk factors present, cardiac symptoms): noninvasive stress testing; echocardiography	Significant cardiac disease
Risk of pulmonary disease: pulmonary function studies	Significant pulmonary disease

HIV, human immunodeficiency virus.
Modified from Bia M, Gaston RS. Pre-transplant evaluation of the living donor. In: Normal DL, Suki WN, eds. *Primer on Transplantation.* Thorofare, NJ: American Society of Transplant Surgeons; 1998:191.

considerably. This enthusiasm is fed by the safety and efficacy of the procedure comparable to the open technique with attractive benefits for the patient during convalescence. The less morbid approach leads to less postoperative pain and a quicker return to normal activities, and has been reported to increase the number of donations.[113,114] More recent data suggest, however, that small pediatric recipients of adult kidneys removed laparoscopically may be at risk for inferior outcomes (i.e., delayed graft function and early rejection).[115] A relatively low threshold for open donor nephrectomy in these situations seems advisable until more data are available.[116]

The laparoscopic donor nephrectomy procedure has been well described because laparoscopic techniques are commonplace in surgical practice. Antiembolism sequential compression stockings are placed, and the patient is placed in a modified flank position. The abdomen is insufflated with carbon dioxide, and four transperitoneal laparoscopic ports are placed. Access to the retroperitoneum is obtained by reflecting the colon after incising the line of Toldt. The left kidney is gently mobilized, taking care to avoid excessive dissection of the lower pole, which could interfere with ureteral blood supply, and the hilar vessels are dissected to their junction with the aorta or vena cava. The ureter is mobilized with a generous cuff of retroperitoneal adipose tissue to maximize its vascularity.

When the recipient room is ready, the ureter is clipped and divided at the level of the iliac vessels, leaving the proximal end open. Good urine output is documented from the divided ureter and the indwelling urethral catheter. The renal artery and vein are sequentially ligated with a stapler, the vessels are divided, and the kidney is extracted from the Pfannenstiel incision. The kidney is immediately flushed with cold preservation solution, placed in saline ice slush, and delivered to the adjacent recipient room. Hand-assisted laparoscopy also has been described for donor nephrectomy with similarly successful outcomes.[114]

RENAL TRANSPLANTATION

Establishment of Compatibility

The first consideration regarding compatibility concerns the blood group antigen (ABO) system.[117] The blood group polysaccharides are expressed on the endothelium of the allograft, and the presence of preformed antibodies results in hyperacute rejection when incompatibility is present in a fashion analogous to that of hemolytic blood transfusion reactions. These antigens are not genetically linked to HLA, and even in the presence of HLA identity, ABO incompatibility may be encountered. To avoid further disadvantaging group O recipients, who tend to have a long wait for deceased donor allografts,[118] organ procurement agencies have generally restricted the use of organs from deceased donors with blood group O to group O recipients. Living donor compatibility is managed in a fashion analogous to that of blood transfusion as regards the ABO blood group antigens. Blood group D (Rh) has traditionally not been considered to be a clinically relevant histocompatibility barrier in renal transplantation.[117] Studies published in 1998 have shown on multivariate analysis an adverse impact of Rh incompatibility, however, on long-term graft survival.[119]

Occasionally, the urgency of attaining a graft may influence such evaluation. This is particularly true in a patient with compromised dialysis access potential, which, as previously noted, may be particularly problematic in a young child with ESRD who has received urinary reconstruction. Attention has been directed at transplantation across the group A–antigen barrier in the specific setting of the group A_2–antigen subset, which represents approximately 20% of group A donors.[117] Although most experience has been attained in adults, early evidence suggests that group A_2 donor to blood group B or O recipients can be successful in children as well.[120] Occasional accelerated acute rejections have been encountered, however.[121,122] Anti-A IgG titers may influence early and long-term graft survival, and an antibody titer exceeding 1:8 has been reported as a poor prognostic indicator.[123] Otherwise, ABO incompatibilities are strictly avoided. Some experience with ABO-incompatible live donor transplantation was reported in 1998 in an aggressive preparation consisting of transplant recipient plasmapheresis and immunoadsorption before transplantation, local irradiation of the allograft in the early post-transplantation period, and recipient splenectomy at the time of transplantation.[124]

The clinical use of pretransplantation crossmatching to avoid hyperacute and accelerated graft rejection has been extensively reviewed.[125,126] Some center variability exists with respect to performance, interpretation, and the use of this clinical tool. Traditionally, the crossmatching is based on a complement-dependent lymphocytotoxic assay, which may be enhanced in sensitivity by the addition of anti–human globulin. Flow cytometry is a particularly sensitive assay that is complement independent.

Occasionally, a clinically insignificant positive crossmatch is encountered related to the presence of autoantibodies. Because these are often of the IgM isotype, incubation of the patient's sera with reagents such as dithiothreitol or dithioerythritol, which eliminate IgM isotype antibodies, is used to screen for autoantibodies. Because not all autoantibodies are IgM, however, and because not all IgM antibodies are insignificant, autoabsorption and retesting of the resultant autocrossmatch-negative serum for residual cytotoxic reactivity is more definitive. Generally, in the absence of autoantibodies, a positive current sera complement-dependent crossmatch for primary transplants and a positive current or historical sera crossmatch for retransplants are considered contraindications to transplantation. Controversy exists about the significance of a positive flow cytometry crossmatch in the presence of a negative complement-dependent crossmatch in primary transplantations. Flow cytometry may provide a significant benefit, however, in the more complicated setting of retransplantation.

Renal retransplantation is one of the settings in which allosensitization, in this case from a previous kidney graft, can be a significant problem.[59] Other such settings include allosensitization from a pregnancy, exposure to blood products such as blood transfusions, and a prior nonrenal organ transplant. Recipients of such transplants are at risk not only for allosensitization, but also for the development of CKD and ESRD, in large part as a result of long-term use of calcineurin inhibitors for antirejection prophylaxis.[127]

Therapeutic options for allosensitized individuals requiring a kidney transplant include desensitization[57-59] or paired kidney exchange.[128,129] Either approach is labor-intensive and should be performed by centers with sufficient expertise and resources to maximize the likelihood of success. Paired kidney exchange also offers an option for ABO-incompatible donor-recipient pairs.

More generally, matching of HLA antigens has historically been shown to have a significant impact on allograft half-life. More recently, such matching may have become less important because of the increased potency of newer immunosuppressive agents.[130] Nonetheless, the matching process continues to play a role, especially in the allocation of deceased donor kidneys. Nationally, six-antigen–matched kidney sharing has been mandated (approximately 5% of deceased donor renal transplantations). In the absence of a six-antigen match, the grafts are allocated locally based on the quality of HLA antigen matching in addition to the length of wait, the reactivity of the recipient sera to a panel of representative lymphocyte antigens, the recipient's age, and other factors.[10] Donor organs are matched and offered to centers for specific and individual patients based on allocation algorithms that are currently undergoing revisions and refinements. Because of the additional neurodevelopmental advantages of kidney transplantation in children compared with adults, wait-listed members of the former age group are typically given an allocation advantage over the latter.

Accepting the Allograft

Whether or not the kidney is accepted after being offered depends on many considerations. Of primary importance is the general health of the recipient candidate. Intercurrent illness is generally a contraindication to transplantation, especially if it represents an infectious disease. Other considerations include the recipient's age, the donor's age, and the status of the kidney offered. The recipient's family is counseled regarding these variables, allowing them to make an informed decision regarding the proposed allograft.

As reviewed subsequently, recipient candidates of very young age may require a graft of smaller size if a transperitoneal transplantation is obviated by peritoneal obliteration, or if future obliteration is to be avoided. Our institution's experience[131] and the experience of others[132,133] have shown a propensity for inferior transplantation outcomes when kidneys from very young donors (<6 years old, and especially <2 years old) are employed in children. The kidneys from such donors may fare better when placed into adults and, in very young donors, when used en bloc.[134-136] The length of cold ischemia time can be important. Evidence reported in 1999 has shown that a donor older than 50 years and a donor who died from cardiovascular disease are other important independent variables.[137]

Transplantation Process

As mentioned previously, recipients entering the operating room for a kidney transplant should be in their best possible medical condition. Children on dialysis may undergo hemodialysis on the day or peritoneal dialysis the night before their transplant for metabolic control (e.g., to reduce serum concentrations of potassium or blood urea nitrogen), but they should be relatively volume-loaded to facilitate adequate perfusion of the new allograft.[138] Dialysis immediately before transplantation should be performed with an adjusted ultrafiltration goal, possibly requiring an increase in antihypertensive drug therapy to compensate for this adjustment. If hemodialysis is required on the day of transplantation, anticoagulation should also be used sparingly, or not at all, to avoid an increased risk of bleeding during surgery.

The transplantation process begins with the induction of general endotracheal anesthesia. The patient is positioned supine, a catheter is positioned in the bladder, and the bladder is inflated under gravity flow with an antibacterial solution. Central venous access is obtained for purposes of fluid monitoring and medication administration. Rarely, a pulmonary arterial catheter is placed if indicated by primary pulmonary or cardiac disease. A second-generation cephalosporin is administered, and intravenous hydration is undertaken. Red blood cell mass is expanded if indicated by a severely low hemoglobin level.

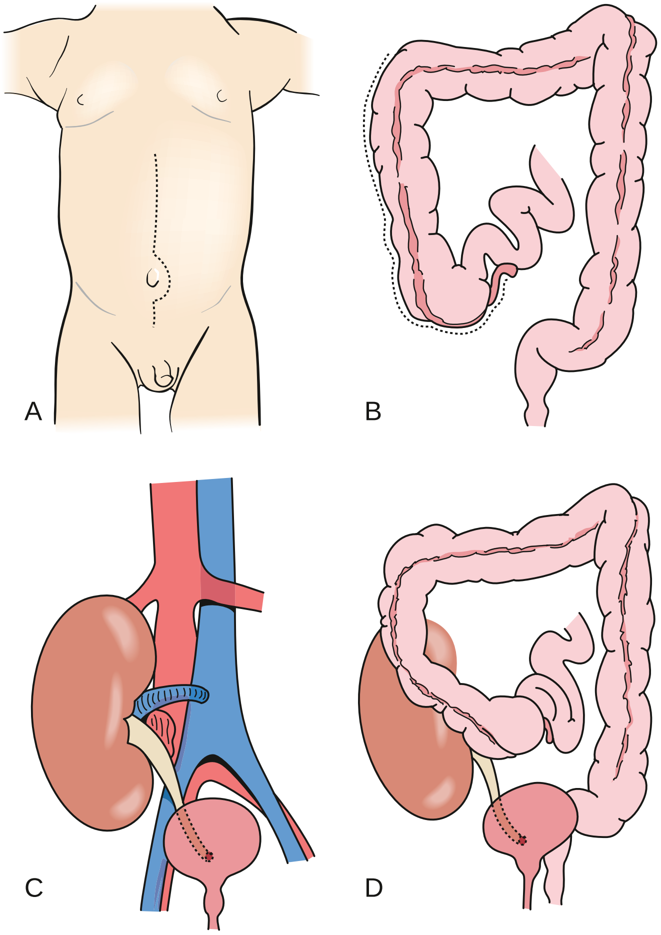

Figure 47-14 Transperitoneal approach to renal transplantation in the infant. **A,** Midline abdominal incision. **B,** Reflection of right colon exposes retroperitoneal anatomy. **C,** Renal vessels are anastomosed directly to the aorta and inferior vena cava. The ureter is implanted into the bladder. **D,** Right colon is repositioned to allow exposure of the lower pole of the graft for subsequent percutaneous biopsy. (From Sheldon CA, Martin LW, Churchill BM. Pediatric renal transplantation. *Surg Clin North Am.* 1985;65:1609.)

The operation is performed through a "hockey-stick" incision, which gives excellent retroperitoneal exposure. Occasionally, a younger recipient may require a transperitoneal approach because of the limited volume of the retroperitoneum. This anatomic decision may be difficult and must be individualized. An attempt is made to place the kidney retroperitoneally to preserve the peritoneal cavity for future dialysis access if needed. General guidelines are as follows: weight greater than 20 kg, retroperitoneal placement; weight 10 kg to 20 kg, pediatric or small adult kidney placed retroperitoneally; weight less than 10 kg, transabdominal placement through a midline incision (Fig. 47-14).[139]

The blood volume of the patient is expanded to a central venous pressure of 12 to 16 cm H_2O, with the expectation that vascularization of an adult allograft would result in the acute sequestration of approximately 250 to 300 mL of blood from the general circulation. The anastomotic sites are chosen, and the venous and arterial trees are carefully mobilized with division of the overlying lymphatic vessels between ligatures. Generally, the anastomosis is placed at the level of the aorta or aortoiliac junction in infants and toddlers, in the common iliac artery in young children, and in the external iliac artery in adolescents and young adults. Vascular control is achieved with the gentle application of vascular clamps or vascular tapes, the venotomy is placed, the recipient vein is injected with a heparin-saline solution, and the venous anastomosis is performed with 5-0 polypropylene (Prolene) suture.

The arteriotomy is made, and the arterial anastomosis is performed with 6-0 Prolene suture. The distal arterial tree is flushed with a heparin-saline solution before the anastomosis. If the aorta is to be occluded, the patient is treated with heparin. Mannitol (0.5 mg/kg) and furosemide (0.5 to 1 mg/kg) are administered before completing the anastomoses. The vascular clamps are removed, with gentle finger pressure applied to the renal artery for 3 seconds to allow clearance of any debris or air pockets before kidney revascularization. An intra-arterial injection of verapamil (0.1 mg/kg not exceeding 5 mg into the upstream recipient artery with the distal recipient artery still occluded) may be performed at this time.

Attention is directed at ensuring that the kidney promptly attains good turgor. Studies have shown the vascularization event to be associated with an abrupt decrease in central venous pressure of 4 to 7 cm H_2O in a small child. Measurements of mean aortic blood flow reveal huge and sustained increases in aortic blood flow in a large graft in a small recipient.[138] Failure to achieve adequate turgor may necessitate additional volume expansion or the addition of inotropic support in the form of low-dose dopamine infusion. Post-transplantation hypotension in the recipient has been shown to be a major risk factor for allograft loss and must be aggressively arrested.

Variations in vascular anatomy may obviate the use of a kidney from a prospective living donor or may create reconstructive challenges in the face of a deceased donor allograft (Fig. 47-15).[140] As previously outlined, in procurement from deceased donors, the kidneys are removed in bloc with the adjacent vena cava and aorta (see Fig. 47-15A). The kidneys are visualized from a posterior perspective, and the aorta is opened in the midline. This is followed by division of the anterior aorta and the vena cava, again in the midline. The kidney is provided with an adjacent segment of aorta and vena cava, which enables a significant degree of reconstructive flexibility. As shown in Figure 47-15B, if a renal vessel is of good dimension, it may be simply divided, spatulated, and anastomosed. If the vessel is small, it may be prepared with a small patch of adjacent aorta or vena cava to facilitate anastomosis and minimize the risk of anastomotic stenosis or thrombosis. Multiple vessels entering the vena cava or aorta in a close cluster may be prepared on a single large cuff of aorta or vena cava (see Fig. 47-15C). If multiple vessels are encountered that enter the vena cava or aorta at sites remote from each other, reconstruction may be needed (see Fig. 47-15D). If both vessels are small, two small patches may be anastomosed to create one larger cuff for anastomosis. If a dominant artery is encountered with a second smaller but important artery, an end-to-side anastomosis is undertaken. This type of vascular reconfiguration is tremendously enhanced by the use of an operative microscope.[141] Occasionally, an extremely short renal vein is encountered. Usually, generous mobilization of the recipient venous tree is sufficient to enable a tension-free anastomosis. When this is impossible or is insufficient, the renal vein may be extended by tubularizing adjacent flaps of vena cava (see Fig. 47-15E).

Ureteral implantation into the bladder may be performed either transvesically (Paquin) or extravesically (detrusorrhaphy). Advantages of the extravesical approach (Fig. 47-16) include a shortened operating time, a very low incidence of anastomotic obstruction, and, most importantly, a dramatic reduction of postoperative hematuria and urinary extravasation. This is particularly advantageous in a young recipient whose urethra is sufficiently small to require a small-caliber catheter that may be easily occluded, even by a relatively small blood or fibrin clot. Ureteral implantation is considerably more critical in a child, in whom the incidence of dysfunctional voiding pathophysiology is particularly high.

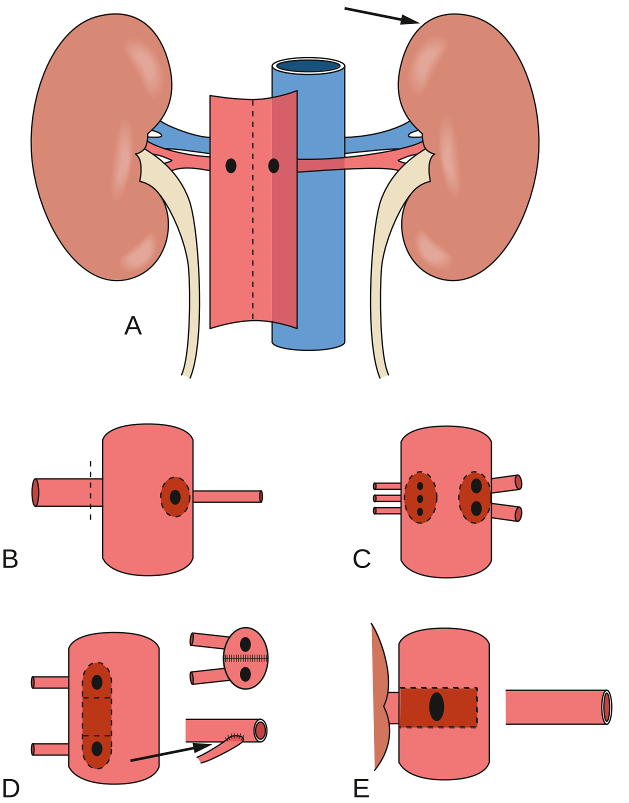

Figure 47-15 **A-E,** Management of variations in renal vascular anatomy (see text). (Adapted from Sheldon CA, Martin LW, Churchill BM. Surgical perspectives in pediatric renal transplantation. In: Gillenwater JY, Grayhack JT, Howards SS, Duckett JW, eds. *Adult and Pediatric Urology.* Chicago: Year Book Medical Publishers; 1995.)

An attempt is made to place the anastomosis lateral on the bladder where the bladder wall is less mobile, and a ureteral tunnel length-to-ureteral diameter ratio of 4:1 is sought (see Fig. 47-16A). The detrusor is incised, and a plane is developed between the detrusor and the underlying bladder uroepithelium. A small defect is created distally in this mucosal trough, and a spatulated anastomosis is performed (see Fig. 47-16B). The ureter is advanced distally with the first suture placed (see Fig. 47-16C). As the remainder of the muscular defect is closed over the ureter to create a nonrefluxing implantation, a small bite of ureter is taken with every other or every third suture to prevent slippage of the ureteral anastomosis within the tunnel and ultimate erosion of the valvular mechanism over time (see Fig. 47-16D). Because ureteral obstruction (e.g., from anastomotic edema) or extravasation represents potentially devastating complications, an internal indwelling stent is often advantageous in the early postoperative period.

Postoperative Care

In addition to general perioperative care, which may require efforts at circulatory, respiratory, and nutritional support, postoperative care of the transplant recipient includes

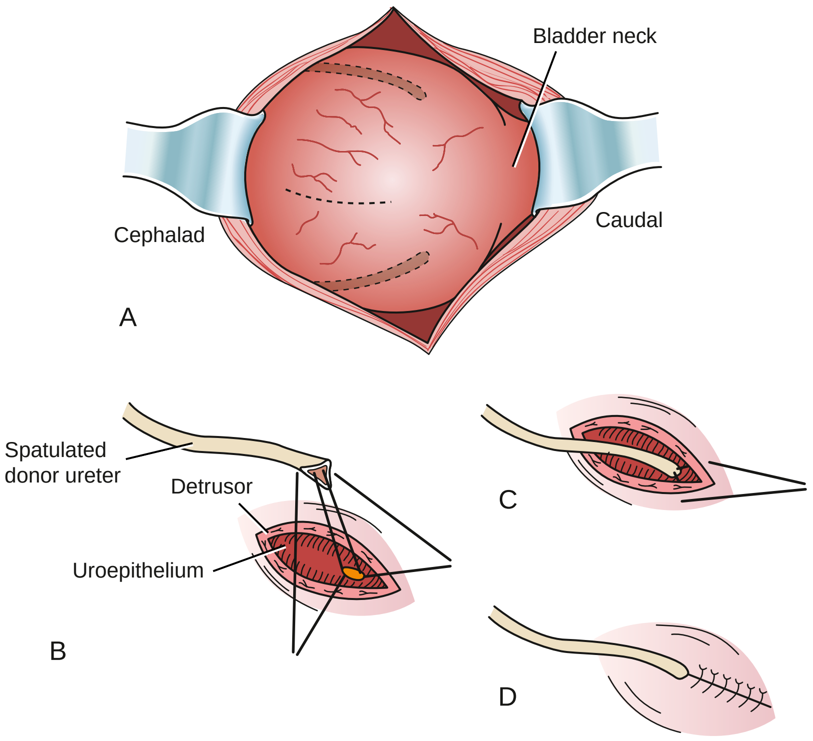

Figure 47-16 **A-D,** Technique for extravesical ureteral implantation (see text).

immunosuppression and often unique approaches to fluid and electrolyte management. Fluid and electrolyte management is challenging and is approached by replacing insensible loss (calculated) and urine output measured on a volume-for-volume basis. It is crucial to realize that the hourly urine output may approach the patient's blood volume in some circumstances, particularly when an adult allograft is placed into an infant. This situation creates a tremendous opportunity for major fluid and electrolyte disturbances, which must be anticipated and prevented.

Table 47-10 outlines the **present immunosuppression** protocol of the Children's Hospital/Medical Center of Cincinnati. Generally, immunosuppressive therapy is in constant evolution to achieve the best possible antirejection prophylaxis without an unacceptably high incidence of overimmunosuppression or other drug-related toxicities.[142] In this context, immunosuppressive protocols cannot be administered in a "one-size-fits-all" fashion: First-time white recipients of a living donor kidney who have no evidence of presensitization seem to require less powerful antirejection prophylaxis than recipients of a repeat transplant, especially one from a deceased donor recipient with evidence of presensitization or recipients who are African-American.[143] Additionally, the more recent discovery of genetic polymorphisms and related phenomena affecting drug metabolism and exposure,[144,145] and immunologic responsiveness[146] further undermines the concept of a unified immunosuppressive approach.

It likely behooves transplant programs to adapt flexible immunosuppression protocols that can be tailored to each recipient's perceived risk profile. Theoretically, the development of such protocols is augmented by sufficiently powered multicenter studies, but in view of the small number of pediatric kidney transplants performed at any given time, and given the increasing number of drugs and drug combinations available, such studies are difficult to set up and perform. Additional guidance in the selection of pediatric immunosuppressive regimens is also derived from adult studies and from local practice and experience.

A typical protocol to be used initially in pediatric kidney transplantation currently consists of triple therapy with a calcineurin inhibitor, an antiproliferative agent, and steroids, possibly paired with a course of induction with a nondepleting anti–T cell antibody (Table 47-10). The doses and target levels of these agents are geared toward the recipient's estimated risk for acute rejection, balanced against side effects and other potential disadvantages associated with the use of these agents. More recent efforts by various groups have broadened further the available choices for initial immunosuppression: They now include complete steroid avoidance, induction with alternative antibody preparations, and introduction of a new class of maintenance immunosuppressants, the inhibitors of the mammalian target of rapamycin (mTOR), largely to reduce the use of calcineurin inhibitors, which carries a substantial long-term risk of nephrotoxicity.[142,147]

Hypertension frequently occurs or, if preexisting, worsens in the immediate post-transplant setting for several reasons, including liberal fluid management (see earlier) and treatment with high doses of corticosteroids. Although mild blood pressure elevations above the patient's pretransplant range may be temporarily desirable to enhance perfusion of the new allograft, more pronounced hypertension, especially if it is causing symptoms, should be treated expeditiously. In this setting, calcium channel antagonists are particularly safe and effective, although attention needs to be paid to the interference of some of these agents, particularly verapamil, diltiazem, amlodipine, and nicardipine, with calcineurin inhibitor metabolism.[143] When transplant function has stabilized, the same group of agents may be particularly beneficial,[148,149] although angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should also be considered, especially if there is evidence of chronic allograft nephropathy (CAN) (see later).[150,151]

Hypophosphatemia and hypomagnesemia can occur quickly after transplantation. The former is largely due to

Table 47-10 Typical Immunosuppression Protocol for Pediatric Kidney Transplant Recipients

Induction*	Maintenance†
Nondepleting anti–T cell antibody	
High-dose steroids	Tapered steroids
Calcineurin inhibitor (tacrolimus)	Modest-dose calcineurin inhibitor
Antimetabolite (mycophenolate mofetil)	Mycophenolate mofetil

*Weeks/months post-transplant.

†An inhibitor of the mammalian target of rapamycin, such as sirolimus (rapamycin) or everolimus, can be added or substituted for any one of the three maintenance agents based on center practice.

"hungry bones" in the presence of a well-functioning kidney and frequently requires phosphorus supplementation for several months. The latter is associated with calcineurin inhibitor, especially tacrolimus, therapy, and may require supplementation, especially if clinical symptoms of hypomagnesemia are present.

Infection prophylaxis against bacterial, viral, and fungal pathogens is part of essentially all routine post-transplant medication regimens. Antibiotic coverage is typically provided perioperatively to prevent wound infections and then transitioned to a prophylactic regimen against UTIs and *Pneumocystis carinii* infection. Specific guidelines have been developed for antiviral prophylaxis in the post-transplant setting.[152] This antiviral prophylaxis is largely directed against cytomegalovirus and usually prescribed based on each patient's risk profile, as determined by his or her and the donor's history of cytomegalovirus exposure, and by the strength of immunosuppression used. No convincingly effective prophylactic regimens are currently available for the prevention of Epstein-Barr virus (EBV) infection. Because many pediatric transplant recipients are EBV-naive, and many adult donors carry EBV, primary EBV infection of transplanted children via the graft is a considerable problem, especially because EBV can drive the development of post-transplant lymphoproliferative disorder (PTLD).[153] Lastly, antifungal prophylaxis is typically provided during the first several months after transplantation (i.e., while the degree of immunosuppression prescribed is considerable). Numerous centers also "recycle" the full spectrum of infection prophylaxis during and after episodes of acute rejection requiring enhanced immunosuppressive therapy.

Gastrointestinal prophylaxis against steroid-associated gastritis and ulcer disease is typically given in the form of a histamine H_2 receptor blocker. At our center, recipients are tried off these agents when they are taking all their medicines by mouth and if they are free of gastrointestinal complaints.

APPROACH TO EARLY GRAFT DYSFUNCTION

Graft dysfunction immediately after transplantation is suggested by lack or decrease of urine output and by absence of the expected decrease in serum creatinine. Initial nonfunction (i.e., the complete absence of urine production) is very concerning because it could be caused by thrombotic obstruction of arterial blood flow to the graft. Initial nonfunction requires immediate diagnostic evaluation and subsequent correction if the transplant is to be salvaged. Many centers perform a Doppler ultrasound evaluation or a nuclear scan of the transplant immediately after skin closure or on arrival in the postoperative care unit, at least if there is no sufficient urine output attributable to the transplant. Along these lines, many recipients still have their native, often urine-producing, kidneys at the time of transplantation, making interpretation of urine output immediately after transplantation sometimes challenging. If blood flow to the transplant is adequate, acute tubular necrosis should be suspected as an alternative cause of initial nonfunction, especially in deceased donor transplants. In recipients who are not at particularly increased immunologic risk, hyperacute rejection is unlikely. Lastly, the possibility of complete urinary tract obstruction needs to be excluded by ultrasound in this scenario.

In grafts with initially acceptable urine production, but a subsequent decrease in output, additional possibilities need to be considered, including low intravascular volume, rejection, and acute calcineurin inhibitor toxicity. Low intravascular volume can be diagnosed if a fluid challenge sufficient to increase central venous pressure results in restitution of adequate diuresis, and acute calcineurin inhibitor toxicity is indicated by elevated trough levels (e.g., tacrolimus concentrations >15 to 20 ng/mL). Early rejection can be difficult to diagnose because its recognition usually requires a kidney biopsy, which may be risky in a fresh transplant. Different types of rejection may need to be distinguished because they require different therapeutic responses. Especially in presensitized recipients, acute rejection not only can be cellular but also antibody-mediated (i.e., humoral), necessitating the initiation of plasmapheresis and potentially other specific therapeutic measures instead of treatment for cellular rejection, which consists of steroid pulses or the application of depleting anti–T cell antibody products. Cellular and humoral rejection can coexist, and the recognition of humoral rejection requires special studies on the biopsy material (i.e., staining for C4d) and the blood (i.e., identification of antidonor antibody).[154]

Additional complications resulting in early impairment of graft function are thrombosis of the renal vein or one of its major branches, obstruction of urine flow (e.g., by a blood clot), and urinary leakage (e.g., from an unsatisfactory ureteral anastomosis). Ultrasound and nuclear scan are useful tools to identify these problems.

TRANSITION TO OUTPATIENT MANAGEMENT

After successful kidney transplantation, children typically spend at least 1 week in the hospital recovering from the procedure. During this time, their fluid, caloric, and medication intake is adjusted to their outpatient regimen, and central lines and bladder catheters are removed in most cases.

Transition to outpatient care occurs on an individualized basis, depending on medical and geographical aspects. Local patients continue to be seen frequently at the transplant center, initially several times a week, whereas others, who may have been referred for transplantation from a nephrology care provider further away, may return rapidly to care rendered by that provider. Recipients with complex lower urinary tracts also require long-term urologic follow-up.

After hospital discharge, patient management is largely focused on maintaining graft function without overly toxic or complex treatment regimens, to facilitate maximal patient rehabilitation with regards to growth and development, allowing as "normal" a childhood as possible with regular school participation and sports or other extracurricular activities.

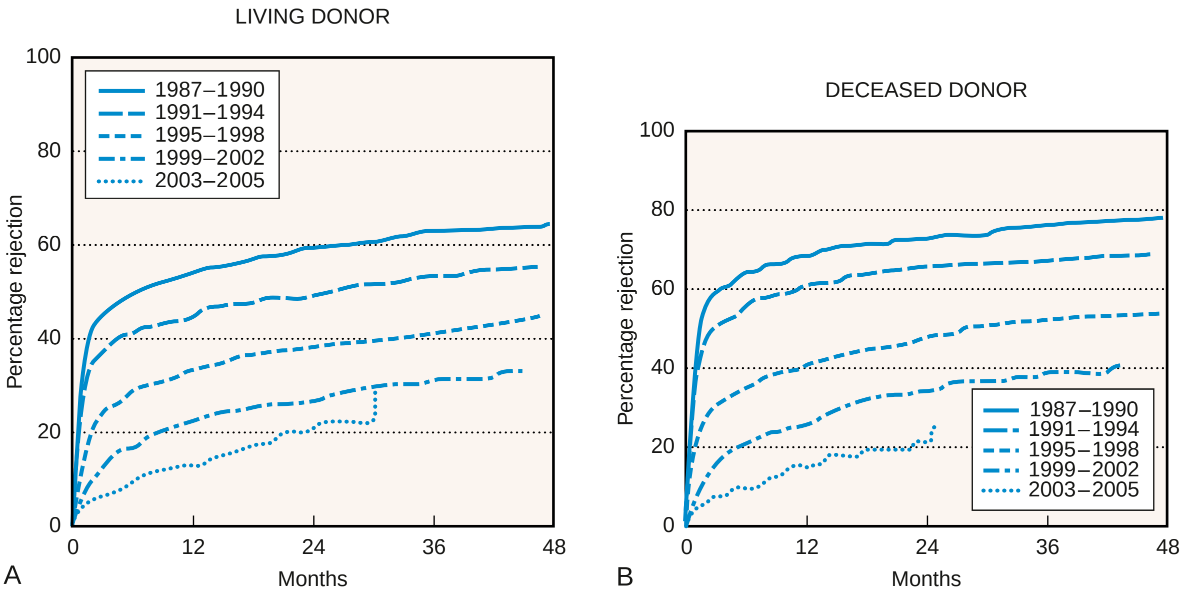

Figure 47-17 Time to first rejection by transplant era and allograft source (**A,** living donor; **B,** deceased donor). Note that most rejection episodes occur in the first post-transplant year. (From the 2006 NAPRTCS Annual Report.)

Historically, maintenance of graft function largely consisted of the prevention or at least prompt recognition and treatment of acute rejection. With the application of the latest immunosuppressive strategies, the incidence of acute rejection in the first 6 to 12 post-transplant months should be approximately 15% (Fig. 47-17), and the most common reason for rehospitalization of pediatric kidney transplant recipients is now infection and not rejection.[155] These trends, paired with the almost inevitable development of CAN over time[142,147] and the considerable incidence of PTLD,[156] imply that numerous patients (likely excluding patients at high immunologic risk) may currently be overimmunosuppressed. Discussions and efforts are under way to develop more appropriate regimens for rejection prophylaxis, taking into consideration an individualized risk profile based on various graft and recipient factors (see earlier).

Generally, prudent combinations of several antirejection agents, adjusted based on various parameters as outlined earlier, remain the mainstay of immunosuppressive therapy as long as the advent of protocols capable of inducing true immunologic tolerance remains uncertain. Evidence is beginning to accrue in support of long-term administration of mycophenolate mofetil as the antiproliferative immunosuppressant agent of choice as part of such a combination (Table 47-11).[157] Rapamycin also has gained acceptance as a valuable addition to the current immunosuppressive armamentarium in various settings including pediatric kidney transplantation.[158,159] Although difficult to tolerate by many patients, this agent seems to have some potential, especially with regard to calcineurin inhibitor–associated nephrotoxicity[158,159] and possibly malignancy,[160-162] including EBV-driven PTLD.[163]

SURGICAL COMPLICATIONS OF TRANSPLANTATION

The incidence of surgically significant renal transplantation complications, as encountered in four large pediatric series, is diagrammed in Figure 47-18.[164-167] Technical complications occurred in 13% of transplantation procedures, of which 35% resulted in graft loss. Urologic complications (excluding uncomplicated UTIs) occurred in 5.6% and consisted primarily of urinary extravasation, ureteral anastomotic obstruction, ureteral necrosis, and symptomatic VUR. Urologic complications resulted in allograft loss in 31% of cases.

Renovascular complications were encountered in 5.5% of cases. Excluding primary allograft nonfunctioning and renal artery or vein thrombosis with documented patent vascular anastomoses, a 3.2% incidence of technical vascular complications was encountered, and consisted of renal artery stenosis, renal artery thrombosis, and renal vein thrombosis. Eighty-six percent of all vascular complications and 74% of technical vascular complications resulted in allograft loss. As expected, renal artery and vein thrombosis have particularly high incidences of graft loss and may have a technical cause (e.g., anastomotic defect, vascular angulation, or compression) or a nontechnical cause (e.g., a low flow state, intimal injury from harvesting, cannulation, or existing donor vascular disease). Renovascular stenosis may be managed by percutaneous transluminal angioplasty,[168] although some centers have reported greater success with primary surgical reconstruction.[169]

Wound complications occurred in 4.2% of patients and consisted primarily of lymphocele, hemorrhage, and infection. Wound infection and lymphocele resulted in no graft loss. Hemorrhage was associated with a 44% incidence of graft loss. Allograft rupture was reported in 2.4% of patients and was generally associated with aggressive rejection. In several instances, hemorrhage was controlled, and the kidney was surgically salvaged, resulting in a 57% incidence of acute graft loss. Long-term follow-up has revealed a very poor prognosis, however, for significant long-term function.[166,167]

Urolithiasis occasionally can complicate the allograft in adults,[170,171] and children.[172,173] Such cases may be particularly challenging because of the increased level of difficulty experienced with endoscopic stent placement and ureteroscopy. A multifactorial etiology of urolithiasis has been shown with a low urine output, an elevated excretion of calcium, and prevalence of uric acid.[174] UTI, alkaline pH, hypocitraturia, hypomagnesuria, and hypophosphaturia also seemed to be operative. Hyperparathyroidism was encountered in 36%.

Table 47-11 One-Year Graft Survival and Acute Rejection Rate by Graft Source and Transplant Era

Panel A: Percent 1-Year Graft Survival by Donor Source and Annual Cohort Groups

Transplant Year	Living Donor (%)	Deceased Donor (%)
1987-1990	89.4	75.2
1991-1994	91.7	85.2
1995-1998	94	90.5
1999-2005	95.4	93.7

Panel B: 12-Month Probability (%) of First Rejection, by Transplant Year

	Living Donor		Deceased Donor	
Transplant Year	%	SE	%	SE
1987-1990	54.2	1.7	69.1	1.5
1991-1994	44.8	1.5	60.6	1.6
1995-1998	33.4	1.4	40.8	1.7
1999-2002	22.6	1.3	26.8	1.9
2003-2005	13.2	1.9	15.8	2.3

From the 2006 NAPRTCS Annual Report.

Extracorporeal shock wave lithotripsy has been used effectively in the allograft,[175] and endourologic approaches have proved useful for urolithiasis and other upper tract urologic complications.[176]

The significance of VUR has been controversial. When VUR was detected by routine post-transplantation screening, no statistical significance in the survival of patients or grafts was shown for adults[177] or children.[178] The adult series had no patients with greater than grade III reflux, however, and all patients with greater than grade III reflux in the pediatric series received antireflux reconstruction. In most cases, reflux is detected because of a clinical event. Decreasing allograft function may prompt an ultrasound examination that shows hydronephrosis, suggesting the possibility of reflux. Alternatively, pyelonephritis or recurrent UTI prompts a study. It would seem reasonable that dilating reflux into a previously nondilated collecting system, when ureterovesical junction obstruction has been excluded, should be considered clinically significant. Most often, the underlying problem is occult or incompletely managed bladder dysfunction, and the reflux is controllable by management directed at the bladder. Dilating reflux associated with nonimmune allograft injury or infection (particularly pyelonephritis) in the absence of a dysfunctional bladder should be considered for correction. Dilating reflux in young recipients is associated with a definite risk of pyelonephritis and subsequent allograft injury.[179] VUR also has been implicated as a significant etiologic factor for hypertension on long-term follow-up.[180]

MEDICAL COMPLICATIONS AND LONG-TERM ASPECTS OF TRANSPLANTATION

Current survival statistics (Fig. 47-19; see Fig. 47-13 and Table 47-11) document excellent short-term and medium-term patient and graft survival for children with kidney transplants, overall comparable to the outcomes of adult kidney transplantation. An exception to this generally encouraging progress is the inferior early survival of grafts, especially from deceased donors, transplanted into infants. This attrition is likely attributable to the increased technical challenges and thrombotic risks associated with such young recipient age. Transplantation is currently avoided by many centers before the recipient has reached a weight of 8 to 10 kg, an approach aided by more recent advances in the dialytic and other management of young children with ESRD.[29]

Likely as a major reason for this overall remarkable improvement in outcomes of pediatric kidney transplantation, acute rejection rates have also become largely independent of allograft source and decreased overall (see Fig. 47-17 and Table 47-11), again to rates very similar to those seen in adult recipients. Controversy exists, however, regarding long-term outcomes, largely because of the propensity of the current immunosuppressive protocols to contribute to CAN; cardiovascular disease, which is the leading cause of death among adult kidney transplant recipients,[147,181] and second only to infection as cause of death in pediatric recipients (NAPRTCS 2006 Annual Report); PTLD; post-transplant growth failure (discussed earlier); and bone disease.[182]

CAN, which essentially results in gradual scarring of the allograft tissue, is caused by a combination of immunologic and nonimmunologic insults and eventually strongly associated with chronic calcineurin inhibitor exposure.[142,147,183] Also referred to as “chronic rejection” because of its immunologic component, CAN causes approximately half of all transplant losses in children and represents the most common cause of such loss in this population (NAPRTCS 2006 Annual Report). CAN has been extensively reviewed, and various strategies for its prevention and management have been suggested, including minimization of calcineurin inhibitor exposure.[147,183]

Based on the 2006 NAPRTCS data, cardiovascular disease causes 15.5% of all deaths in pediatric kidney transplant recipients. Cardiovascular morbidity in this patient population is very prevalent and begins relatively early during CKD and long before actual transplantation.[184,185] Before and after transplantation, the CKD-specific and transplant-specific risk factors for cardiovascular disease are superimposed on more traditional

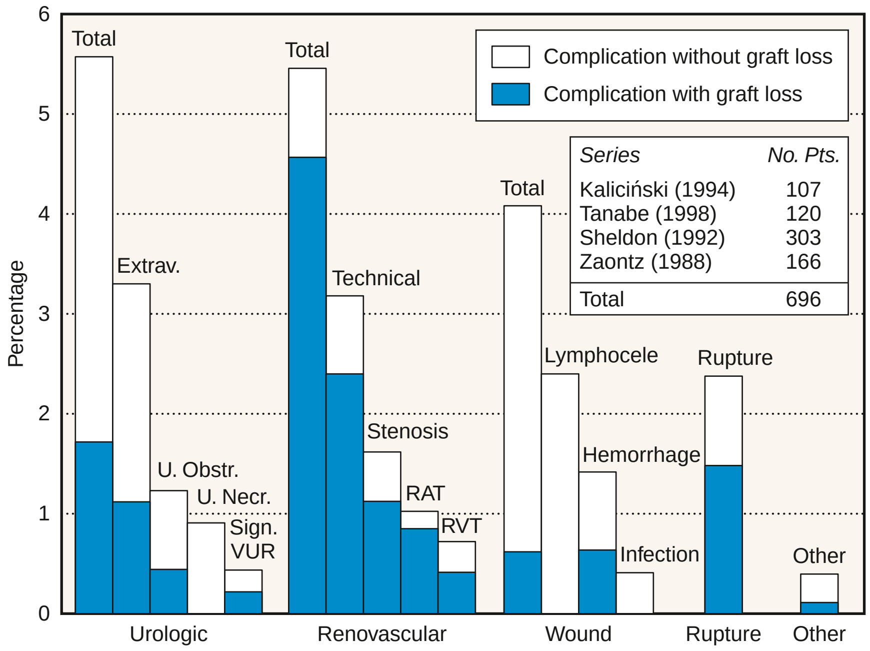

Figure 47-18 Incidence of surgically significant pediatric renal transplantation complications. Graft loss percentages include patient death and transplantation procedures aborted because of complications. Extrav., extravasation; RAT, renal artery thrombosis; RVT, renal vein thrombosis; Sign. VUR, significant vesicoureteral reflux; U. Necr., ureteral necrosis; U. Obstr., ureteral obstruction.

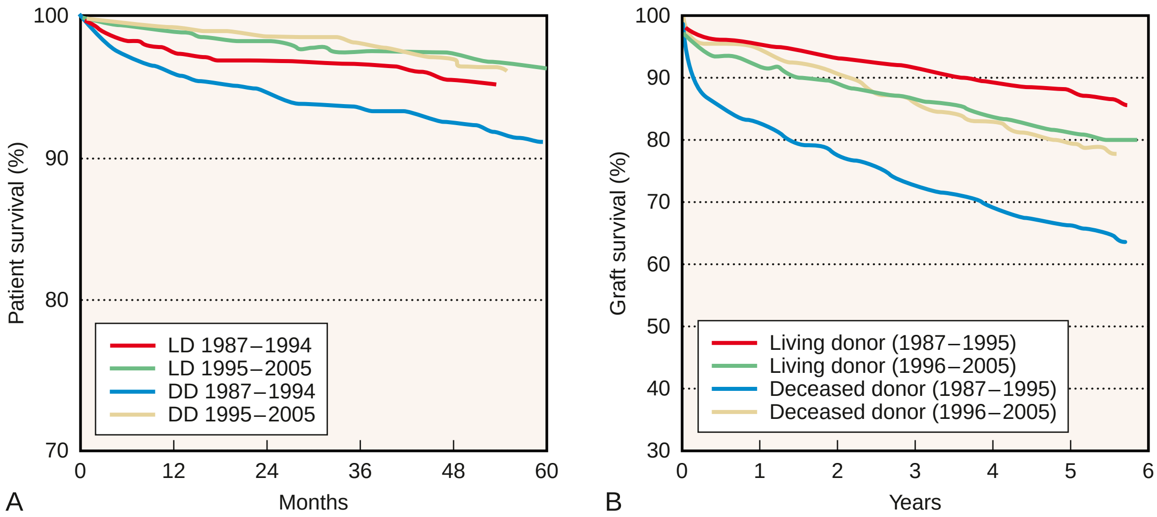

Figure 47-19 Five-year patient **(A)** and kidney graft **(B)** survival by transplant era and graft source. DD, deceased donor; LD, living donor. (From the 2006 NAPRTCS Annual Report.)

risk factors to add up to a tremendous odds ratio for cardiovascular morbidity and mortality in children with ESRD.[184,185]

Malignancies currently cause slightly more than 10% of all deaths in pediatric kidney transplant recipients (NAPRTCS 2006 Annual Report), and more than half of these malignancies are some form of PTLD.[186] Many of these cases of PTLD are driven by EBV,[187] which in many cases is introduced via an EBV-positive transplant from an adult donor into an EBV-naive immunosuppressed pediatric recipient.

Although more recently half-lives of more than 35 years for renal allografts from living donors have been predicted by some,[188] the challenge for the future is to develop better long-term care regimens for kidney transplant recipients with special emphasis on the avoidance of CAN and cardiovascular disease[142] and PTLD. Such optimistic half-life predictions are not shared by others,[189] and even a transplant half-life of 30 or 40 years would theoretically be insufficient for children because a substantial number of transplants would still be lost early during their adulthood. There is already a growing population of patients at especially high immunologic risk—patients who have lost a previous kidney transplant or are recipients of another organ transplant, and have developed renal failure from chronic calcineurin inhibitor toxicity or for other reasons. These patients not only compete with first-time transplant candidates for organs, but they also have a high incidence of sensitization from their previous or ongoing allograft exposure and are more difficult to transplant and to manage after transplantation.[57-59]

Another emerging challenge in the medical management of children with kidney transplants is the provision of a meaningful transition from teenage to adulthood, including transfer of transplant-related care to providers for adults. Teenage and the transition phase into adulthood are associated with an increased incidence of adverse outcomes, at least partly as a result of more frequent noncompliance (see Fig. 47-13).[55] Better strategies to enhance compliance during these critical stages in the life of pediatric transplant recipients are urgently needed.

Lastly, adequate living kidney donor follow-up is required because of their increased risk of hypertension and proteinuria several decades after donation.[109] Along these lines, efforts to standardize this follow-up and to create a donor registry are under way in the United States. Some former donors have even lost function of their remaining kidney because of trauma, malignancy, or kidney disease that was not apparent at the time they donated, and these individuals are given very high priority in the organ allocation algorithm currently in place via the United Network for Organ Sharing.

CONCLUSION

Renal transplantation is the treatment of choice for pediatric patients with ESRD, and is associated with excellent short-term and medium-term outcomes, at least in recipients without extraordinary immunologic or other risk factors. In many children receiving a kidney allograft, urologic issues are of special importance before, during, and after transplantation because of the comparably high incidence of urologic disease in this age group. Important current challenges revolve around optimal long-term outcome, specifically CAN and long-term calcineurin inhibitor nephrotoxicity and other complications of prolonged administration of immunosuppressive agents, and compliance.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 48

UROLITHIASIS IN CHILDREN

Henri Lottmann, M. F. Gagnadoux, and M. Daudon

EPIDEMIOLOGY

Urolithiasis in children is considered uncommon in Western countries. No recent data have assessed possible changes in the epidemiology. The overall incidence of stones in children was reported to be less than 2 per 1 million total populations in Great Britain.[1] In Spain, Camacho Diaz and colleagues[2] observed 1 case of urolithiasis among 4500 children admitted to their pediatric hospital. Edvardsson and coworkers[3] reported an annual incidence of kidney stones equal to 5.6 per 100,000 Icelandic children for the period 1995-2000. In the United States, stone disease accounted for 1 in 7600 to 1000 hospital admissions[4,5] in children. More recent reports suggest that urinary calculi are being recognized with increasing frequency.[6-9]

Gender and Age

Similar to in adults, boys are affected more often than girls in Western countries, but significant changes are observed according to age. In Germany, Brien and associates[10] found a male-to-female ratio of 1.5, based on the largest series of stones collected from children ($N = 2134$). In the United States, the male-to-female ratio was reported to be less than 1.5 in two studies.[4,5] In France, the male-to-female ratio among 1091 children with lithiasis was found to be decreasing from 4.73 in infants younger than 2 years old to 0.97 in children older than 14 years.

Stone Location

Stones in children are essentially located in the upper urinary tract. Kidney stones represented 61.1% of stones in the series reported by Gearhart and colleagues,[4] 61.6% of stones in a Spanish study,[2] and 58.8% of stones in our 1091 cases. Bladder stones are currently found in only 5% to 10% of cases. Spontaneous passage of calculi, in most cases coming from the upper urinary tract, seems to be frequent (35% to 50%), although less than observed in adults (70% to 75%).

Stone Composition

Figure 48-1 illustrates typical calculi found in children. Differences in stone composition are noted according to the published series. Calcium oxalate was found as the main component in 65% of cases in Germany,[10] 39% in Spain,[2] and 26% to 65% in the United States.[4,11,12] Among 1091 pediatric stones, we found calcium oxalate as the main component in 34.7%. Calcium and magnesium phosphates represented 43.5% of stones in Spain,[2] whereas calcium phosphate stones represented 40.1% of stones in our series, in which struvite was present in 287 calculi (26.3%).

Stone composition differed according to sex and age of patients (Table 48-1). In children younger than 5 years, carbapatite was the main component, predominantly in boys. Struvite was present in 40.8% of stones in boys and in 27.6% in girls, but it was the main component in only 6.4% of all calculi. Calcium oxalate was significantly less frequent in boys (12.2% versus 23.8% in girls; $P < .01$). Purines were found in about 8% of cases in both sexes, essentially as ammonium urate. The proportion of calcium phosphate stones was especially high in infants of both sexes (see Table 48-1). In patients older than 5 years, calcium oxalate was the main component in about 50% of cases in both sexes. Struvite, carbapatite, and purine stones were less frequent. In all, calculi of metabolic origin were more frequent in children older than 5 years. Changes in stone composition may be observed according to the period of stone collection. In recent years, the proportion of calcium phosphate stones related to metabolic disorders, especially hypercalciuria, has increased, and infectious stones were less frequent than observed at the beginning of the 1990s.

PATHOPHYSIOLOGY

Steps of Stone Formation

The first condition of stone formation is supersaturation of one or more substances excreted in urine. Supersaturation may be calculated from the urine pH and concentration of solutes using EQUIL 2, a computer program initially developed by Finlayson and coworkers in Florida and updated in the 1990s.[13] Crystallization in urine results from an imbalance between promoters and inhibitors.[14] Promoters are mainly calcium, oxalate, phosphate, and urate. Inhibitors are substances that counteract the effects of promoters. Citrate, pyrophosphate, glycosaminoglycans, and glycoproteins are the most effective. Urine pH and ionic strength also strongly influence the crystallization risk.[15] Because of a higher content of citrate in urine and urinary macromolecules, especially glycosaminoglycans, children are less prone than adults to form urinary calculi.[16,17]

Several stages are involved in lithogenesis. First, supersaturation may induce crystal nucleation in the lumen of the tubules, especially for calcium phosphates. Second, the crystals may aggregate or fix to the membrane of tubular cells because of their charges. A customary site for the nidus of stone is the renal papilla. The subsequent stone growth depends on supersaturation levels induced by metabolic disorders and dietary habits. Low diuresis always is an aggravating factor, which highly contributes to high concentrations of solutes and subsequent crystallization.[18]

Infection-Induced Lithogenesis

The most common lithogenic process resulting from urinary tract infection (UTI) involves urease-producing microorganisms. Gram-negative bacteria, such as *Proteus* species, are able to hydrolyze urea, producing ammonium and carbon dioxide and increasing urine pH and bicarbonate content.[19] The main biochemical effect is alkalinization of urine and high levels of struvite and calcium phosphate supersaturation, which frequently induce the crystallization of several compounds, including struvite, carbapatite, and ammonium urate when hyperuricosuria is present. Another consequence is the high carbonate content of carbapatite, which is highly suggestive of such a lithogenic process, even if struvite is not present in

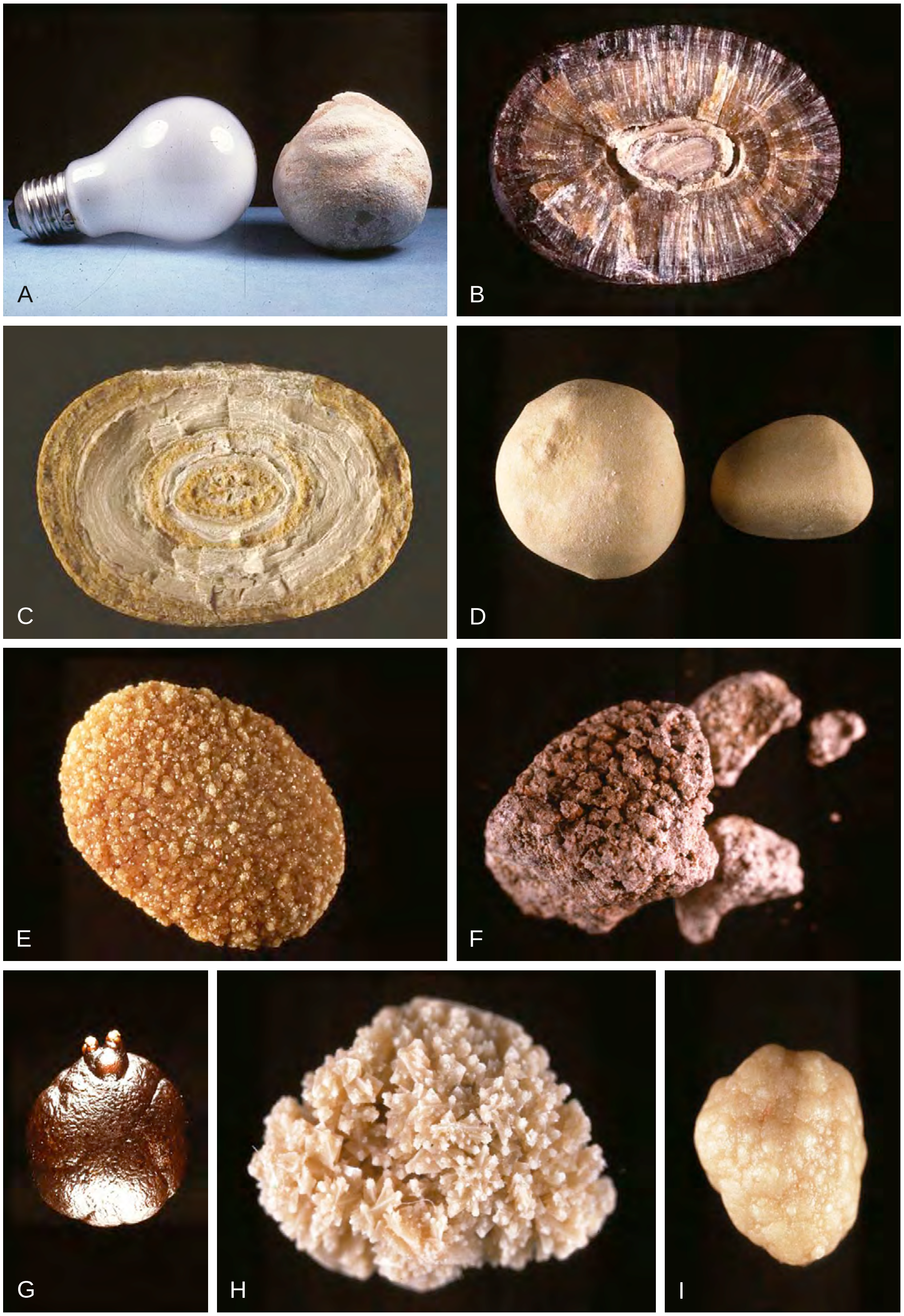

Figure 48-1 Typical aspect of some urinary stones found in children. Stone fragility: + (resistant) to ++++ (easy to fragment with extracorporeal shock wave lithotripsy). **A,** Very large bladder endemic stone surgically removed in Laos. The stone came from a 20-year-old man. It contained ammonium urate, calcium phosphates, and struvite. Fragility: ++++. **B,** Section of an endemic bladder stone surgically removed from a 7-year-old Tunisian boy. The stone was composed of calcium oxalate monohydrate surrounding a core made of ammonium hydrogen urate. Fragility: +. **C,** Another section of an endemic bladder stone from Thailand. The stone was made of a mixture of uric acid, ammonium hydrogen urate, and calcium oxalate. Fragility: +++. **D,** Renal infection stones from an infant with an ureteropelvic junction stenosis. The stone composition was carbapatite mixed with struvite and amorphous carbonated calcium phosphate. Fragility: ++++. **E,** Pure cystine bladder stone discovered in a 3-year-old girl. Fragility: + to ++. **F,** Pure dihydroxyadenine stone secondary to a complete adenine phosphoribosyltransferase deficiency in a 9-year-old boy. Fragility: +++. **G,** Pure calcium oxalate monohydrate from a 13-year-old child presenting with very low diuresis (0.5 L/day) and imbalanced diet including high animal protein and chocolate intake and low dairy products. The stone morphology is Ia. Note the dark color, resulting from mainly the slow growth of the stone and fixation of urinary pigments. Fragility: +. **H,** Pure calcium oxalate dihydrate in a 10-year-old boy with hypercalciuria. The morphology is typical of type II, which is the main morphologic type found in hypercalciuria. Fragility: ++++. **I,** Pure calcium oxalate monohydrate spontaneously passed in a 9-year-old girl with primary hyperoxaluria type I. Note the budding surface and the very light color of the stone, which is typical of type Ic, found in heavy hyperoxaluria. Fragility: ++.

Table 48-1 **Main Components of Urolith According to the Sex and Age of the Patients (*N* = 1091)**

	Boys				**Girls**			
	<2 yr (*n* = 241)	**2-≤5 yr (*n* = 154)**	**5-≤10 yr (*n* = 131)**	**≥10 yr (*n* = 204)**	**<2 yr (*n* = 51)**	**2-≤5 yr (*n* = 54)**	**5-≤10 yr (*n* = 94)**	**≥10 yr (*n* = 162)**
Ratio M/F	4.73	2.85	1.39	1.26				
Phosphates	77.2	50.7	22.1[a,b]	21.6[a,b]	60.8	31.5[c]	23.4[a]	18.5[a]
Carbapatite	71.8	39	15.3	14.2[a]	47.1[f]	25.9	16	14.8[a]
Other calcium phosphates	5.4	11.7	6.9	7.4	13.7	5.6	7.5	3.7[d]
Struvite	4.2	9.1	16.8	10.3[e]	5.9	9.3	2.1[f]	4.9
(Presence of struvite)	41.5	39.6	30.5	15.2[a,b]	27.5	27.8	9.6[f]	10.5[d,g]
Calcium oxalates	3.7	25.3	42.8	50[a,b]	9.8	37[f]	48.9	62.4[a,g]
Whewellite (COM)	1.2	11	17.6	26.5[a,h]	2	20.4[d]	19.1	37.7[a]
Weddellite (COD)	2.5	14.3	25.2	23.5[a,i]	7.8	16.7	29.8[d]	24.7[d]
Purines	5.8	10.3	5.3	5.5	9.8	9.3	7.5	0.6[d]
Ammonium urate	3.3	8.4	3	2[i]	5.9	5.6	5.3	0.6[e]
Uric acid	2.5	1.3	1.5	2.5	3.9	3.7	1.1	0[e]
Other purines	0	0.6	0.8	1	0	0	1.1	0
Proteins	5	3.3	7.6	6.4	5.9	3.7	6.4	5.6
Cystine	1.2	1.3	1.5	3.9	2	9.3[j]	4.3	5.6
Drugs	2.1	0	3	1.5	2	0	3.2	0.6
Miscellaneous	0.8	0	0.8	1	3.9	0	4.3	1.9

[a] *P* < .0001 versus <2 yr.
[b] P < .0001 versus 2-≤5 yr.
[c] P < .05 versus <2 yr.
[d] P < .01 versus <2 yr.
[e] P < .05 versus <2 yr.
[f] P < .001 versus boys of the same age group.
[g] P < .01 versus 2-5 yr.
[h] P < .001 versus 2-5 yr.
[i] P < .05 versus 2-5 yr.
[j] P < .01 versus boys of the same age group.
COD, calcium oxalate dihydrate; COM, calcium oxalate monohydrate.

the stone. The main microorganisms able to hydrolyze urea involved in stone processing are summarized in Table 48-2.

Besides the changes in the urine biochemistry, microorganisms are able to form a biofilm that covers the epithelium and makes easier the adherence of bacteria and fixation of the crystals.[20] The biofilm also protects the microorganisms against the action of antibiotics, making it difficult to treat chronic UTI effectively when stones or fragments are in the urinary tract. More recent work suggests that nanobacteria, which are able to crystallize apatite, could be involved in the first stages of stone formation, especially as concerns numerous calcium stones assumed to be of metabolic origin.[21]

Endemic Urolithiasis

In developing countries, pediatric urinary stone disease occurs more commonly than in industrialized nations, with particular patterns including bladder location, high male preponderance, and frequency of ammonium hydrogen urate in stones.[22,23] Stones from the bladder have been reported in

Table 48-2 **Main Urease-Producer Microorganisms**

Urease-Producer Microorganisms	**Occurrence of Strains Producing Urease (%)**
Proteus	90-100
Pseudomonas	32
Providencia	90-100
Klebsiella	63
Other microorganisms	
Serratia marcescens	29
Staphylococcus aureus	80
Staphylococcus epidermidis	88
Corynebacterium urealyticum	100
Ureaplasma urealyticum	100

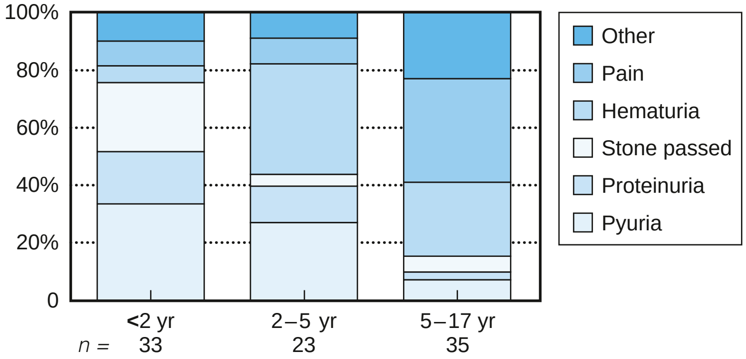

Figure 48-2 Presenting symptoms of urolithiasis in childhood according to patient age.

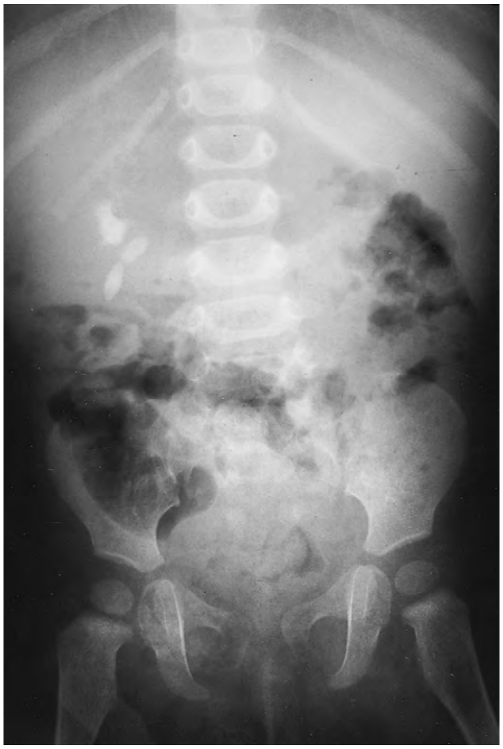

Figure 48-3 Typical aspect of kidney stones on an abdominal plain radiograph.

26% of pediatric stone formers in Turkey[22] and 67% in India.[24,25] Because of changes in socioeconomic level and progressive improvement of medical care available to the population, the occurrence of bladder stones seems to be decreasing.[2] To date, calcium oxalate is the main component of urinary calculi from children living in most developing countries.[26,27] The stones are mainly formed by calcium oxalate surrounding a core of ammonium hydrogen urate, which is in contrast to stone composition observed in Western countries, where calcium oxalate and calcium phosphate calculi commonly develop from a calcium phosphate nucleus.

Metabolic and dietary factors are involved in so-called endemic urolithiasis. Simultaneous hyperuricosuria and low phosphorus excretion are required to induce ammonium urate crystallization. Acute or chronic diarrhea, a cereal-rich or vegetable-rich diet often with high oxalate content, low protein and phosphorus intake, high uric acid excretion, and low diuresis are usually involved in the mixed ammonium urate–calcium oxalate stones that form the main part of endemic calculi. Phosphate supplementation and consumption of dairy products correct crystalluria and prevent stone formation in most patients.

DIAGNOSIS

Clinical Presentation

The symptoms of urolithiasis in children differ from the symptoms observed in adults; in particular, children with stones rarely present with typical renal colic. The presenting symptoms vary according to the child's age.[11] In infants, UTI (usually with *Proteus*) and passing of stones in diapers are the usual manifestations. In young children, hematuria and pyuria are the main symptoms, whereas in older children, abdominal pain (of various localization) and hematuria are the most frequent presenting signs (Fig. 48-2). Urolithiasis in children is commonly discovered by microscopic or macroscopic hematuria, and the presence of stones must be sought in any child with isolated hematuria.

Imaging

Imaging is essential at all steps of the management of urolithiasis: diagnosis, treatment, and follow-up. The principles are the same as in adults; however, external radiation delivered to children should be a constant concern and limited to the strict minimum necessary, considering that patients with urolithiasis are subject to repeated imaging procedures during treatment and follow-up.

Diagnosis of the Presence of Calculus in the Urinary Tract

When a stone is suspected, the combination of an abdominal plain x-ray (kidney, ureter, and bladder [KUB]) (Fig. 48-3) and urinary tract ultrasound scan allows the diagnosis in most cases. Most calculi are radiopaque and visible on the plain x-ray; however, not all opacities projecting on the expected location of the urinary tract are stones, not all stones are radiopaque, and a stone can be missed in case of bowel distention, as often associated with renal colic. Ultrasound provides an additional noninvasive exploration; the stone has a characteristic appearance of a bright hyperechoic structure that reflects most of the sound wave resulting in a echo-free shadow behind it (Fig. 48-4). The accuracy of ultrasound depends on the operator and equipment, and ultrasound cannot detect ureteral calculi except at proximal and distal extremities; however, most ureteral calculi are either proximal or distal. Ultrasound was found by Diament and Malekzadeh[28] to be more sensitive than KUB (84% versus 54%) in detecting calculi; however, KUB was superior for identifying ureteral stones.

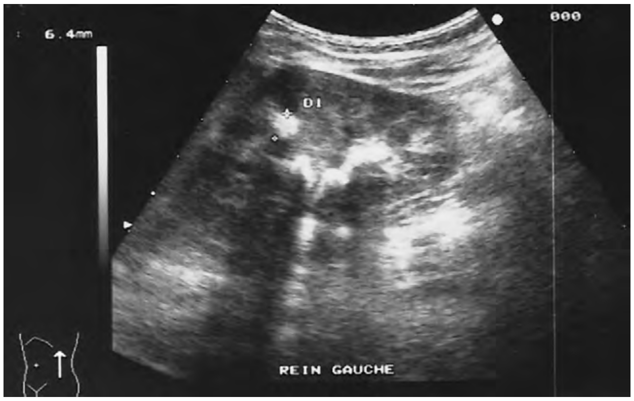

Figure 48-4 Ultrasound shows a stone as a typical bright hyperechoic structure with an echo-free shadow behind it.

A KUB film and urinary tract ultrasound together allow an accurate diagnosis of around 90% of urinary calculi.[4,29] These modalities also provide information about the stone (size and number) and its composition according to its degree of opacity. Ultrasound also provides information about the renal parenchyma and the eventual dilation of the collecting system.

An intravenous pyelogram (IVP) is the study of choice for the very rare calculi not seen on the KUB film or ultrasound, particularly ureteral calculi.[30] An IVP provides morphologic and functional information (Fig. 48-5). Non–contrast-enhanced computed tomography (CT) also can be used to diagnose renal calculi; all stones are much more dense than any other lesion within the collecting system,[31] and each type of stone has its own density (e.g., cystine 100 to 300 Hounsfield units, calcium salts 400 to 600 Hounsfield units) (Fig. 48-6).[32] A subsequent injection of contrast medium can provide functional information and allow additional IVP films to be performed to appreciate the morphology of the collecting system.

CT scan is probably the most sensitive way to detect urinary tract calculi. Use of CT should be limited in children to difficult cases, however, such as small and faintly opaque ureteral stones, because CT delivers significant irradiation.

At the diagnosis phase, imaging is also essential for the pretreatment evaluation. Various parameters influence the choice of treatment, including the characteristics of the stone, its exact location, and underlying abnormalities of the collecting system. Functional information concerning the affected kidney and contralateral kidney may prove to be important for the final treatment decision.

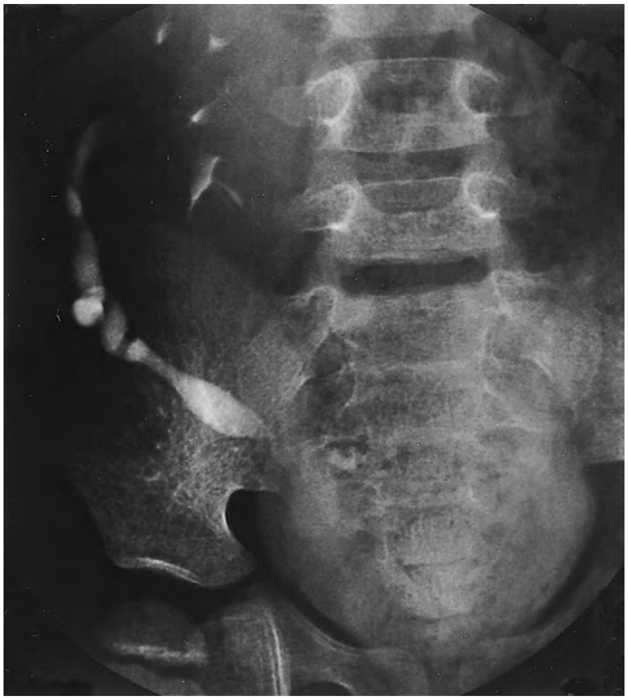

Figure 48-5 IVP of a kidney transplant shows a stone at the ureterovesical junction.

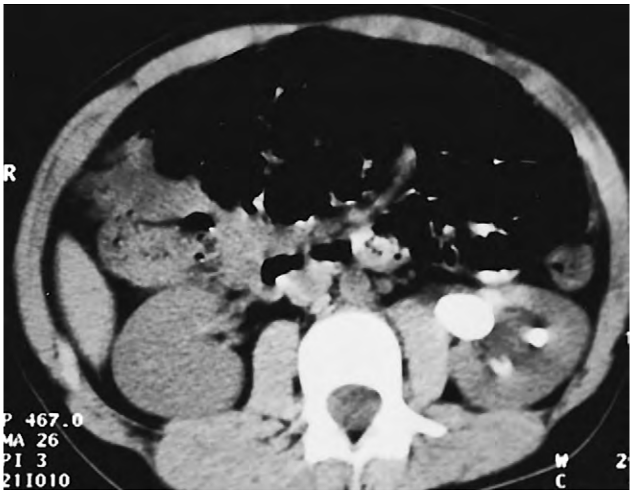

Figure 48-6 Non–contrast-enhanced CT scan shows multiple cystine stones in the left kidney.

Nature and Characteristics of Stone

The characteristics of the stone include the number of pieces, the total stone burden, and the degree of opacity. The degree of opacity of a stone depends on its composition. Uric acid is radiolucent except if the surface is secondarily covered with a calcium deposit (Fig. 48-7A); cystine is homogeneously faintly opaque with a regular shape (Fig. 48-7B). Pure struvite is also faintly opaque, but with time incorporates calcium phosphate and becomes more and more opaque and bigger resulting ultimately in a staghorn calculus (Fig. 48-7C). Calcium-containing calculi are the most opaque, especially calcium oxalate (Fig. 48-7D).

The composition of the stone as evoked by its appearance on imaging greatly influences the therapeutic choice. Uric acid is dissolved with alkalinization of urine, but an eventual calcium shell must be fragmented first by extracorporeal shock wave lithotripsy (ESWL). The treatment of struvite or calcium phosphate stone must include antibiotic therapy because these stones are constantly associated with infection. Cystine is particularly difficult to fragment.

Ultrasound and KUB films are generally sufficient to provide these data; however, the exact location of the calculus in the collecting system is better provided by an IVP or a CT scan combined with an IVP. A calculus in a calyceal diverticulum is a poor indication for ESWL. IVP and CT scan also can identify an associated uropathy, such as a ureteropelvic junction (UPJ) obstruction or a megaureter, which may influence the outcome of the treatment (in such situations, ESWL may lead to stone fragmentation, but no elimination of the fragments). The course and morphology of the ureter need to be defined before ureteroscopy, and the exact morphology of the calyceal system needs to be defined before percutaneous nephrolithotripsy (PCNL). Any underlying

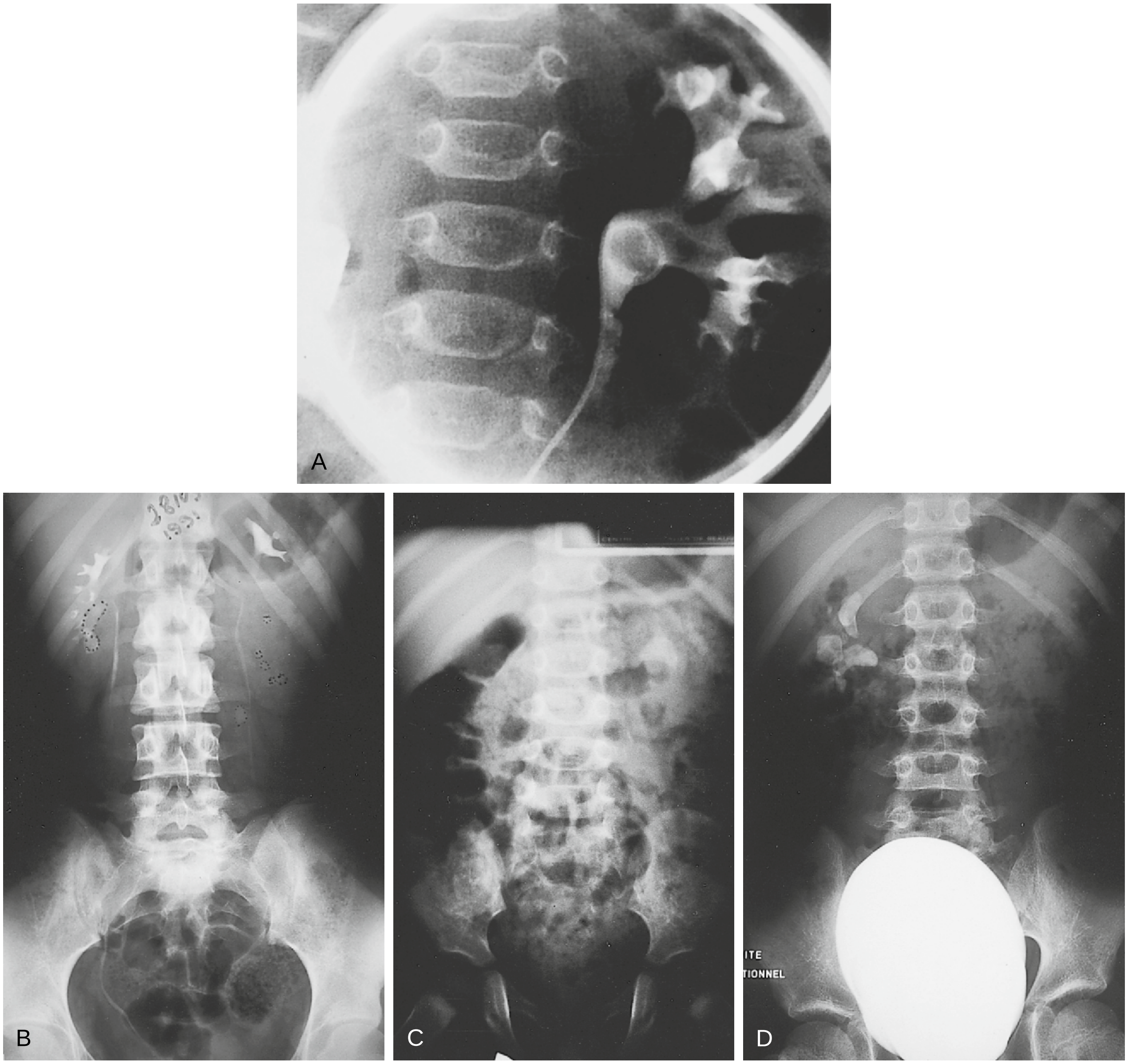

Figure 48-7 **A,** IVP shows multiple uric acid stones in the left kidney in a 6-month-old boy. **B,** Multiple cystine stones in a 13-year-old girl (obstructed lower moiety on the left side). **C,** Struvite left pelvic stone in an 18-month-old boy. **D,** Calcium oxalate staghorn calculus in an 8-year-old boy.

abnormality that may require specific treatment to prevent recurrences must be recognized. It is not always easy, however, to determine if a pelvicalyceal or ureteropyelocalyceal dilation was primary or occurred secondary to an obstructive stone.

Functional information about the affected kidney and contralateral kidney may also be essential in the pretreatment evaluation when the function seems so poor on IVP that a nephrectomy is considered,[33] or when evaluating the parenchymal consequences of a treatment (e.g., ESWL or nephrolithotomy). Radionuclide studies are the most appropriate in such situations.[34]

EVALUATION

The finding or the suspicion of urolithiasis in a child necessitates a comprehensive evaluation to define the causes and consequences of renal stones.

History

In addition to preexisting diseases, all possible causative factors in the child’s history must be sought, such as previous treatment with furosemide in early life or with corticosteroids, or prolonged immobilization or malnutrition. Familial history is also important, as is a history of other stone formers, renal failure, or parental consanguinity suggestive of an inherited metabolic disorder (Table 48-3).

Dietary Information

In children, as in adults, a low urinary volume is a crucial factor for stone development. Normal children, especially young children, rarely feel thirsty, and they often have concentrated urine. If their diet is rich in animal proteins and salt, or if they have a mild metabolic disorder, they may have excessive urinary concentration of stone-promoting substances, such as calcium, oxalate, and purines, which crystallize in insufficiently diluted urine. Dietary information should be sought as a part of the initial evaluation of any child presenting with urolithiasis, regardless of any other etiologic factors that may be apparent.

Laboratory Evaluation

Bacteriology

Urine cytobacteriology is the first step of the laboratory investigation in cases of lithiasis. Because many stones in children are discovered secondary to UTI or hematuria, the diagnosis of infected or infectious stones is rarely missed.

Stone Analysis

Stone analysis is an important step in the etiologic investigation, and is mandatory if a stone is available. The analysis should include morphologic examination and separate identification of the nucleus and surrounding layers. Physical methods, such as x-ray diffraction,[35] infrared spectroscopy,[36,37] or stereomicroscopy,[38] are required for an accurate and clinically relevant analysis. Morphologic examination and infrared spectroscopy currently provide the most useful and accurate information from stone analysis.[36,38] Our group has shown close relationships between morphology and acidification tubular defects, primary hyperoxaluria, or other etiologic factors.[38,39] Differentiation of crystalline species also is important; among calcium oxalate crystalline phases, weddellite is related to hypercalciuria.[38,40,41] Conversely, in the case of hyperoxaluria, whewellite is the main component in about 90% of stones.[42]

Table 48-3 **Data Suggestive of Hereditary Disorder in a Child with Urolithiasis**

Early onset (often in infancy)
Familial history of urolithiasis
Parental consanguinity
Multiple, bilateral or recurrent stones
Associated nephrocalcinosis
Associated renal symptoms—polyuria, acidosis, growth retardation, renal failure
Associated extrarenal symptoms

Crystalluria

A crystalluria study on a first morning urine specimen is often of clinical interest to detect genetic disorders such as cystinuria, adenine phosphoribosyltransferase deficiency, or primary hyperoxaluria; crystals induced by a UTI; and crystals related to specific risk factors for stone disease, such as uric acid, weddellite, brushite, or ammonium urate crystals. The urine pH value must be determined because it is important in estimating the significance of common crystals (Table 48-4). Crystalluria studies are always useful to assess the effectiveness of metaphylactic measures. Usually, there is no recurrence when a follow-up repeat examination of morning urine fails to detect crystals.[43]

Biochemical Analysis

Routine blood sampling includes measurement of serum calcium, phosphate, electrolytes (especially bicarbonates), blood urea nitrogen and creatinine, and uric acid if stones are radiolucent. Routine urinary studies should include

Table 48-4 **Criteria for Interpretation of Crystalluria**

Crystal Identification	Frequent pH Range	Main Clinical Significance
Uric acid dihydrate	<5.3	Acidic urine
	≥5.3	Hyperuricosuria
Amorphous urates	5.2-6.0	Hyperuricosuria
Weddellite (dodecahedrons)	5-7	Hypercalciuria
Whewellite	5-7	Hyperoxaluria
Brushite	<7	Hypercalciuria ± hyperphosphaturia
	≥7	Alkalinizing UTI
Carbapatite, ACCP	≤6.5	Hypercalciuria
	>6.5	Acidification defect, alkalinizing agent, or UTI
Struvite	≥6.8	UTI by urea-splitting microorganisms (*Proteus, Corynebacterium* D2, *Ureaplasma urealyticum*, etc.)
Ammonium hydrogen urate	6.2-6.8	Hyperuricosuria + hyperammoniagenesis + low urine phosphate concentration
	>6.8	Hyperuricosuria + UTI by urea-splitting microorganisms
Cystine	5-7.5	Genetic cystinuria
Xanthine	5-7	Xanthine dehydrogenase deficiency
2,8-Dihydroxyadenine	5-8.5	Homozygous APRT deficiency
Drugs (amoxicillin, ceftriaxone, indinavir, sulfadiazine)	Variable	Low diuresis, high dosage, inappropriate urine pH range

ACCP, amorphous carbonated calcium phosphate; APRT, adenine phosphoribosyltransferase; UTI, urinary tract infection.

(1) 24-hour urine collection for daily volume, osmolarity, and timed excretion of calcium, oxalate, uric acid, and citrate, and urea, creatinine, sodium, and potassium (Table 48-5) (if 24-hour collection is impossible, measurements of calcium-to-creatinine ratio or oxalate-to-creatinine ratio, whose normal ranges decrease from infant age to adult [Table 48-6], are repeated)[44-47]; (2) pH measurement on fresh urine; and (3) cyanide nitroprusside test (Brand test) for cystinuria. A positive test or a clinical presentation suggestive of cystinuria requires urinary amino acids chromatography or cystinuria measurement (see Table 48-5).

MAIN CAUSES OF CHILDHOOD STONES

Depending on the authors and their interest in etiologic investigation, a cause is found in 50% to 90% of cases of childhood urolithiasis in recent series (average 75%).[4,11,25,48-51] Infection and urinary metabolic abnormalities are the main causes of stone formation in children.

Urinary Stasis and Infection

Anatomic Anomalies

Anatomic anomalies of the genitourinary tract are predisposing factors to stone formation. Because of urine stasis, the risk of UTI is enhanced, as is the crystallization risk induced by metabolic disorders. According to the literature, anatomic anomalies are found in 15% to 33% of children with urolithiasis.[2,5,52] UPJ obstruction, megaureter, and vesicoureteral reflux (because of secondary UTI) are the three most frequently encountered anomalies associated with stone disease in children.[11,52] As emphasized by several authors, however, anatomic anomalies are associated in 70% to 80% of cases with metabolic disorders that are the main factors involved in stone formation in these patients.[1,5,53]

Urine stasis in a neurogenic bladder or in urinary diversion is also a frequent cause of stone formation.[11,54] In urinary diversions or bladder augmentations with sigmoid colon or, more frequently, ileal conduit, acidosis induced by bicarbonate secretion from intestinal mucosa is a factor favoring stone formation through hypercalciuria. Other renal structural abnormalities leading to some degree of stasis, such as medullary sponge kidney, dominant polycystic kidney disease, or horseshoe kidney, may also be complicated by urolithiasis.

Infection-Related Stones

Infection-related stones are frequently seen in children, particularly in infants and children younger than 5 years. Among 1091 children with urolithiasis, we found that 90% of either boys or girls younger than 5 years presented with UTI or had a past history of UTI. In patients older than 5 years, the incidence of UTI decreased to 42% in boys and 50% in girls.

As described earlier, the role of urease-forming bacteria, mostly *Proteus*, in the development of many stones is clear, particularly as regards phosphate stones; however, it is often difficult to determine whether a bacterial infection is the primary cause or complicates a preexisting stone, particularly in cases of obstructive uropathy. If a stone is available, its sequential analysis by physical methods is especially useful in such cases. Based on stone analysis, the presence of struvite is not the only criterion for asserting that an infection process caused the stone. Other criteria should be considered, such as the carbonate rate of carbapatite, the protein content, and some other characteristics of the stone.[40]

Metabolic Lithiasis

Hypercalciuric Lithiasis

Hypercalciuria is present in a child if at least two or three measures of 24-hour calcium excretion, at intervals of some weeks, exceed 4 mg/kg (>0.1 mmol/kg). When timed urine samples are not possible, the calcium-to-creatinine ratio may be used. The normal limit of this ratio is much higher in infants than in older children and adults (see Table 48-6).[44-47] In addition,

Table 48-5 Normal Daily Excretion of Urinary Solutes in Childhood

Calcium	<4 mg/kg/24 hr (0.1 mmol/kg/day)
Oxalate	<0.5 mmol/1.73 m^2/24 hr (45 mg/day)
Cystine	<0.13 mmol/1.73 m^2/24 hr (31 mg/day)
	<0.1 mmol/g creatinine (24 mg/g creatinine)
	<0.03 mmol/mmol creatinine
Urate	< 4 mmol/1.73 m^2/24 hr
Citrate	>1.5 mmol/1.73 m^2/24 hr
Magnesium	>4 mmol/1.73 m^2/24 hr
Phosphate	Variable

Table 48-6 Normal Values of Calcium and Oxalate-to-Creatinine Ratios in Childhood

Age	Calcium (mmol/mmol [mg/mg]) (mean/95th percentile)	Oxalate (mmol/mmol) (mean/95th percentile)
<6 mo	0.7/2.4 (0.25/0.86)	0.14/0.36
7-12 mo	0.5/1.7 (0.2/0.6)	0.11/0.23
1-5 yr	0.4/1.1 (0.14/0.4)	0.08/0.18 (1 yr)
		0.04/0.10 (<5 yr)
5-12 yr	0.35/0.7 (0.12/0.25)	0.04/0.08 (≥5 yr)
		0.03/0.07 (12 yr)

Data from references 44-47.

any value measured within 6 to 8 weeks after an ESWL session cannot be considered.

Hypercalciuria is a major stone-promoting factor in children as in adults, and may be of various etiologies. Hypercalciuria may proceed from anomalies in calcium renal excretion or intestinal absorption or bone resorption, which may be associated. These anomalies may be genetic, acquired (often iatrogenic), or idiopathic.[55]

Secondary Hypercalciuria

Among iatrogenic causes for hypercalciuria, some (e.g., vitamin D excess, high-dose steroid therapy) have almost disappeared because of better knowledge of this complication and adequate prevention, whereas new causes have appeared. Currently, the most frequent cause of drug-induced hypercalciuric urolithiasis in children is the prolonged use of furosemide, theophylline, or corticosteroid therapy in premature infants.[56-58] Prematurity also seems to be a risk factor for urolithiasis.[58-60]

Hypercalciuria may also result from nutritional causes, such as excessive intake of calcium, or more often of proteins and sodium, with a diet poor in potassium and phosphate. An example of a nutritional cause of lithiasis is the "ketogenic diet" (high proteins/low carbohydrates) increasingly used in refractory pediatric epilepsy, which induces hypercalciuria and hypocitraturia through acidosis.[61] In cases of long-term immobilization, hypercalciuria resulting from excess bone resorption may cause stone formation, particularly in cases of insufficient hydration in mentally disabled children.

Primary hyperparathyroidism is very rare in children, but may be observed in adolescents.[62] The parathyroid hormone concentration must be checked if calcemia is increased.

Genetic Hypercalciurias

Genetic diseases that alter renal tubular reabsorption of calcium are numerous.[63] The most frequent one in childhood used to be distal tubular acidosis (Albright acidosis), in all its genetic varieties. In this disorder of urine acidification, hypercalciuria and hypocitraturia are the consequence of blood acidosis; in the absence of alkalizing treatment, it leads to medullary nephrocalcinosis and nephrolithiasis originating from the papilla. Owing to earlier diagnosis and better management of these children, the incidence of lithiasis in this disease has decreased considerably in the last decades.

Hypercalciuria is also a major symptom of the two main forms of neonatal Bartter syndrome, but associated polyuria reduces the stone risk. In X-linked nephrolithiasis, or Dent syndrome, renal stones are a major symptom in adults, but are rarely observed in childhood. Stones may also develop in rare diseases, such as familial hypomagnesemia with hypercalciuria, autosomal dominant hypocalcemia, familial isolated hypoparathyroidism, Lowe syndrome, Wilson disease, glycogen storage type I, and tyrosinemia type I.[63] Among genetic diseases increasing calcium intestinal absorption, stones have been observed in hypophosphatemia due to *NPT2a* gene mutation and in glucose-galactose malabsorption.[63]

Idiopathic Hypercalciuria

When no etiology or genetic disease is found, and hypercalciuria persists despite adequate diet, hypercalciuria is considered idiopathic. The proportion of idiopathic hypercalciurias among childhood lithiasis series decreased as several genetic causes were described, and the increased knowledge of the many genes involved in calcium metabolism will most likely allow further division of idiopathic hypercalciuria into several genetic varieties. The diagnosis of idiopathic hypercalciuria cannot be accepted without a comprehensive evaluation, including familial inquiry and investigation of the primary mechanism—excessive intestinal absorption or renal leak.[63]

Hyperoxaluric Lithiasis

Hyperoxaluria is defined as daily excretion of oxalate greater than 0.5 mmol/1.73 m^2 body surface area or, in infants in whom 24-hour diuresis is unavailable, as a urinary oxalate-to-creatinine ratio greater than the normal limit for age (see Table 48-6). Secondary hyperoxaluria is exceptional in children, and when oxalate stone and hyperoxaluria are found in a stone-forming child, primary hyperoxaluria, a severe hereditary disease leading to end-stage renal failure, should always be suspected, particularly in consanguineous populations.[64] In addition, a milder idiopathic hyperoxaluria seems able to induce recurrent stone formation in some children.

Primary Hyperoxaluria

Primary hyperoxaluria type I (PH1), the most frequent and most severe form of inherited hyperoxaluria,[65] is an autosomal recessive disorder of glyoxylate metabolism in the liver that is caused by a defect in the enzyme aniline/glyoxylate aminotransferase (AGT).[66] The first manifestations of the disease usually occur in infancy or childhood as a recurrent whewellite urolithiasis or nephrocalcinosis or both.[39,67] In the absence of adequate management, end-stage renal failure ultimately develops. Oxaluria, in children with PH1 without advanced renal failure, frequently reaches values greater than 1 mmol/24 hours. Associated hyperglycolaturia (normal value <80 mg or 900 μmol/1.73 m^2/day) is present in two thirds of cases. Direct measurement of the defective enzyme AGT through liver biopsy or molecular diagnosis of *AGTX* gene mutations is possible in a few laboratories in the world.[68]

Primary hyperoxaluria type II, which is rarer than PH1, results from the absence of glyoxylate reductase, which has also a D-glycerate dehydrogenase activity. Hyperoxaluria is associated with excessive urinary excretion of L-glyceric acid. Diagnosis can be confirmed by measurement of glyoxylate reductase activity in a liver biopsy specimen.[69]

Secondary Hyperoxaluria

The main cause of secondary hyperoxaluria in children is *enteric hyperoxaluria,* which results from intestinal malabsorption of fats and bile acids that, by binding calcium, result in increased oxalate absorption.[70] This complication, which has been described in inflammatory bowel diseases, ileal resection, and cystic fibrosis, can be avoided by adequate dietary prescriptions. Absence of the anaerobic intestinal oxalate-degrading bacterium *Oxalobacter formigenes* may also play a role in some cases of secondary hyperoxaluria, as has been shown in cystic fibrosis patients, in whom the development of renal stones is common.[71,72]

Mild Idiopathic Hyperoxaluria

Mild idiopathic hyperoxaluria (>0.5 mmol/day), sometimes associated with hypercalciuria, was found in 10% to 20% of stone-forming children in our experience, and in some other series.[11,73] Its pathophysiology was unknown, but half of our patients had siblings or parents with a history of stone formation.

Cystine Lithiasis

Cystinuria is a hereditary disorder involving the transport of cystine and other dibasic amino acids (lysine, arginine, ornithine) through the renal proximal tubular and intestinal epithelium. Because of the low solubility of cystine in urine, its increased excretion results in recurrent urolithiasis, often beginning in childhood. Type I cystinuria, caused by mutations in the *SLC3A1* gene on chromosome 2, is a recessive disease in which the parent carriers show a normal cystine excretion. In the non–type I form, caused by mutations in the *SLC7A9* gene on chromosome 19, heterozygotes are usually (but not always) mildly cystinuric.[74] Cystinuria accounts for 5% to 10% of cases of pediatric urolithiasis,[5,11,50,51,75] and it frequently is revealed during infancy by pyuria, hematuria, or stone passing. Cystine stones are usually faintly radiopaque. Cystinuria must be suspected in any child with lithiasis; before the availability of stone analysis or crystalluria study, the diagnosis could be suspected from urinalysis indicating a positive sodium nitroprusside test (red color of sulfhydryl compounds) and had to be confirmed by urinary amino acid chromatography and cystine dosage (>200 mg or 0.8 mmol/1.73 m^2/day, or >0.1 mmol/g creatinine, usually approximately 1 mmol/g).

Purine Stones

Uric Acid Stones

Uric acid stones depend on acidic urine pH and hyperuricosuria. The fractional excretion of uric acid is high in newborns and regularly declines from birth to puberty, in parallel with a linear increase in plasma urate,[76] explaining the possible risk of uric acid stones in infants who present with tubular immaturity or with a risk of low diuresis and acidic urine because of diarrhea. Uric acid stones, still observed in developing countries,[48,49] are currently rare in children in Western countries.[50]

In acute acquired hyperuricemia secondary to cellular lysis in myeloproliferative or lymphoproliferative syndromes, uric acid stones may develop if adequate preventive measures of hyperhydration and alkalinization are not applied. Among genetic disorders, hereditary renal hypouricemia, an isolated defect of urate tubular handling owing to mutation in the gene of tubular exchanger URAT1, may induce stones through increased urate clearance.[77] Several inborn errors of purine metabolism result in hyperuricemia and hyperuricosuria. Hypoxanthine guanine phosphoribosyltransferase deficiency, an X-linked disorder, is an infrequent cause of uric acid nephropathy and stone disease in boys.[78] The deficiency may be complete (Lesch-Nyhan syndrome), or incomplete with only gross uric acid overproduction and excretion. Purine phosphoribosylpyrophosphate synthetase superactivity is another infrequent X-linked inherited cause of uric acid overproduction.[78]

Other Inherited Purine Disorders

The most frequent inherited purine disorder is deficiency in adenine phosphoribosyltransferase (APRT), an autosomal recessive disease caused by a mutation of the *APRT* gene located on chromosome 16.[78] In APRT deficiency, adenine is oxidized by xanthine dehydrogenase to 2,8-dihydroxyadenine (DHA), which is the less soluble purine at any pH. Often DHA stones are mistaken for uric acid stones because they are radiolucent. When undiagnosed, APRT deficiency may have deleterious consequences on renal function.[78]

Xanthine dehydrogenase deficiency is another rare autosomal recessive disease that may induce xanthine stones and renal insufficiency in children and adults.[78] The xanthine dehydrogenase enzyme (previously named xanthine oxidase) catalyzes the conversion of xanthine and hypoxanthine to uric acid. Diagnosis is based on the coexistence of hypouricemia and hypouricosuria.

Drug-Induced Lithiasis

In children, stones made of crystallized drugs are rare because the main drugs responsible for this complication, triamterene and sulfadiazine, have little use at this age.[79] Stones made of ceftriaxone are common in the gallbladder, but are uncommon in the urinary tract.[80] Amorphous silica has been found in the core of stones in some infants who received formula-thickening powders containing silica.[81] Stones made of antiproteases (e.g., indinavir), which are frequent in adults with human immunodeficiency virus infection,[82] are very rarely observed in children.

Idiopathic Urolithiasis

In some children, the etiologic investigation remains negative, and stone does not recur; in these patients, stone formation was probably caused by transitory urologic, metabolic, or dietary factors that had already disappeared by the time of stone discovery. In such cases, stone analysis by physical methods may be useful to identify the risk factors that were involved in stone formation. In children with recurrent stones, it is exceptional not to find a cause, and the diagnosis of pediatric idiopathic lithiasis should not be accepted before a comprehensive evaluation, including stone analysis, has been made.

MANAGEMENT OF PEDIATRIC UROLITHIASIS

The finding of urolithiasis in a child does not always involve surgical treatment. Spontaneous passage of stones is common, especially in infants. In some diseases (e.g., cystinuria, uric acid stones), medical treatment alone may dissolve small stones. Every child with urolithiasis requires medical management by the pediatrician, preferably a pediatric nephrologist. The main objective of medical management is to avoid formation of new stones and impairment of renal function, first by increasing urine dilution, which is always necessary, and, if possible, by correcting the metabolic abnormalities promoting lithogenesis.

Nonspecific Measures

Pain Alleviation

Not all children with stones complain of pain, particularly younger children, and when pain is present, it more frequently has an abdominal localization than typical renal colic symptoms. Pain treatment should be adapted to the degree and type of pain, and the use of nonsteroidal anti-inflammatory drugs may be necessary in case of renal colic.

Anti-Infectious Treatment

Antibiotic treatment is mandatory in case of infected urine; however, urine sterilization is often difficult to obtain as long as numerous stones fill the urinary tract, and becomes possible only after stone elimination. In case of persisting urinary tract obstruction or stasis, prolonged antibiotic prophylaxis is often necessary to avoid recurrence of infection-associated stones.

Hydration and Diet

Except in the case of acute ureteral obstruction, urine dilution is the basic measure to help dissolution of microlithiases and to prevent recurrence. Fluid intake should be 1.5 to 2 L/m^2/day, throughout the day *and night*. Compliance to this prescription is rarely obtained from children and adolescents. When hyperhydration is crucial in young children, such as in primary hyperoxaluria, nasogastric tube hydration, particularly during the night, is necessary. Any form of fluid may be used except milk products, tea, and calcium-rich mineral water. Advice should be given to follow a well-balanced diet and particularly to avoid excessive intake of animal proteins and sodium, both of which increase urinary calcium excretion.[55] The same holds true for purines in uric acid stones.

Etiology-Specific Measures

In many cases, treatment of the causative disease is sufficient to prevent stone recurrence. This includes treatment of recurrent infection or of urologic abnormalities, and adequate management of acquired or genetic metabolic disorders.

Metabolic Causes

PRIMARY METABOLIC UROLITHIASIS

Hypercalciuria. Dietary measures should be prescribed first. A low-calcium diet is never advisable in children. A low calcium intake (<700 mg/1.73 m^2/day) seems to increase the risk of stone formation.[83] Milk product intake that is clearly excessive for the child's age must be reduced to a normal amount. The reduction of sodium intake is much more efficient to decrease urinary calcium excretion, and a moderate restriction should be prescribed, and a moderate protein restriction in children with a high appetite for meat.[84] In contrast, increased potassium intake has been shown to reduce calciuria by increasing the urinary sodium-to-potassium ratio in hypercalciuric children.[85] Dietary potassium supplementation is easy to prescribe to children.

When dietary measures fail to decrease urinary calcium to a normal range, hydrochlorothiazide (0.5 to 1 mg/kg/day), generally efficient in reducing calciuria, may be prescribed with caution (regular plasma ionogram checking is needed) in children with renal tubular leak. An advantage of hydrochlorothiazide is it increases diuresis and fluid intake.

Primary Hyperoxaluria. In primary hyperoxaluria, the prevention of nephrocalcinosis and iterative nephrolithiasis is crucial because it may prevent the eventual development of end-stage renal failure.[86] This prevention must be initiated as soon as possible after birth to preclude any calcium oxalate deposits within the kidneys.

The first measure consists of massive hyperhydration (>3 L/m^2/day); infants and young children require fluid administration through a nasogastric tube, at least during the night. When children with PH1 are submitted to surgical procedures or to ESWL, it is crucial to continue massive hydration intravenously during anesthesia to avoid intrarenal oxalate precipitation induced by dehydration.

The second treatment is pyridoxine, which is a cofactor of glyoxylate metabolism. About 20% of patients with PH1 have a pyridoxine-sensitive enzymatic defect and experience a decrease of more than 30% in oxaluria with vitamin B_6 supplementation.[87] Pyridoxine sensitivity must be tested in each patient, with increasing dosage every 4 weeks from 5 to 20 mg/kg/day. Treatment must be continued if efficacious.

The third measure is to prescribe magnesium or citrate (0.15 g/kg), or both, to decrease urinary calcium oxalate supersaturation.[88,89] There are few palatable forms of citrate for children, however, and in our experience it may be replaced by bicarbonate with equivalent efficacy.

Mild Hyperoxaluria. In addition to increasing fluid intake (1.5 to 2 L/m^2/day), which is the most important measure, patients with mild hyperoxaluria may benefit from medications aimed at decreasing calcium oxalate supersaturation, such as magnesium, potassium citrate, or both.[89] In hyperoxaluric children, the intake of oxalate-rich foods (e.g., spinach, rhubarb, sorrel, beetroot, tea, chocolate) must be reduced.

CYSTINURIA

The prevention of stone recurrence in children with homozygous cystinuria is a particular challenge for the pediatric nephrologist or urologist because of the tendency toward high recurrence and the difficulty for children to comply endlessly with preventive treatment.[90] The basic preventive measures are simple: high fluid intake (>2 L/m^2/day) throughout the day and night and permanent urine alkalinization with potassium citrate or bicarbonate (1 to 3 g three to four times a day), with regular urinary pH checking at home aiming to maintain pH at 7.5. Excessive protein and sodium intake should be avoided, particularly at the evening meal. Children rarely consume methionine-rich food (e.g., stockfish, horsemeat, fish eggs); a moderate consumption of eggs should be advised. If these preventive measures are appropriately followed, it is possible to avoid stone formation in most children with homozygous cystinuria before lithiasis development and, in most compliant children, to avoid stone recurrence after stone removal.

In the case of stone appearance or recurrence, sulfhydryl compounds must be added to try to dissolve small stones and to avoid recurrence, by decreasing free cystine via the formation of more soluble complexes with cysteine.[90] Penicillamine (20 to 40 mg/kg) is the most effective, but its side effects (ageusia, cutaneous rash, leukopenia, and proteinuria) limit its use and necessitate close surveillance; α-mercaptopropionyl-glycine or tiopronin (20 to 30 mg/kg) is better tolerated, but seems slightly less effective. Dosage of sulfhydryl compounds must be gradually increased and given in divided doses, with half of the daily dose taken at bedtime because the cystine urinary concentration is maximal during the night. The efficacy of treatment must be monitored at regular intervals by checking the disappearance of cystine crystalluria,[91] urine volume (>1.5 L/m^2/day), urine pH (>7), and free cystine urine concentration (<250 mg/L).

PURINE STONES

General advice in addition to the treatment of all purine disorders is hyperdiuresis and restriction of purine intake because high purine consumption may worsen the clinical symptoms and stone formation.

Uric Acid Stones. Allopurinol is appropriate in all cases of overproduction of uric acid, as in myeloproliferative disorders and their chemotherapy, and in cases of genetic disorders. Allopurinol dosage must not exceed 4 mg/kg to avoid xanthine accumulation and xanthine stones.

Other Purine Stones. In homozygous APRT deficiency, allopurinol is an effective drug to reduce DHA production. Medical management of homozygous xanthine dehydrogenase deficiencies mainly includes high fluid intake (>2 L/day), which is particularly important to prevent stone recurrence. In these two disorders, alkalinization is poorly effective.

Medical Follow-up

Children with stones require close follow-up from the pediatric nephrologist or urologist, with frequent outpatient visits (every 3 or 4 months) because they are unable to adhere continuously to the preventive measures without strict surveillance and emotional support from parents and the physician. Compliance to preventive and therapeutic measures must be assessed at each visit through biochemical urinary monitoring, including, if possible, crystalluria on fresh urine.[43]

Imaging

During conservative treatment or medical management, repeated KUB studies and urinary tract ultrasound examinations generally provide sufficient information for patient follow-up. They must be performed at various intervals according to the causal disease, the clinical symptoms, and the presence or absence of a significant crystalluria. In the absence of symptoms or crystalluria, one imaging examination per year seems sufficient. IVP and CT scan also can be useful to detect residual fragments when necessary.

SURGICAL MANAGEMENT

Rarely, a child with a calculus presents in an emergency situation, such as severe sepsis, colic resistant to medical therapy, anuria, or acute urinary retention—all consequences of the obstruction of the upper or lower urinary tract. In all these conditions, urine drainage above the obstruction level must be obtained by straightforward stone extraction or destruction, or, particularly in case of infection, by the endoscopic or percutaneous insertion of a catheter.

Most of the time, the surgical management of urolithiasis in children is discussed out of a context of emergency. Because of its efficiency and its low morbidity, ESWL should always be considered as the first treatment option; other treatment modalities (i.e., PCNL, ureteroscopy, or open surgery) generally are discussed when ESWL is a poor choice or has failed, or as a combined approach.

Extracorporeal Shock Wave Lithotripsy

ESWL is a perfect example of a fruitful cooperation between the medical and industrial world. Since its introduction into clinical practice in 1980 by Chaussy and associates,[92] it has revolutionized the management of urolithiasis and has become the first option for treatment of most upper urinary tract calculi, dramatically limiting the indications of endourologic procedures and even more open surgery. The technologic improvements of the lithotripters allow most treatments to be performed on an outpatient basis and with reduced anesthesia requirements. First-generation lithotripters were not adapted to the treatment of children, and there was some reluctance to deliver extracorporeal shock waves to developing organs, so the first reports concerning pediatric ESWL series weren't published until 1986.[93] Since then, ESWL has progressively gained wide acceptance as the "gold standard" treatment for upper urinary tract lithiasis in children and in adults. It seems that even better results can be achieved in children than in adults, particularly in the treatment of large stones; with long-term follow-up and morphologic and functional studies, ESWL seems to be at least as safe for children as alternative treatments (endourology or open surgery).

Principles of Extracorporeal Shock Wave Lithotripsy

Chaussy and coworkers[94] created the concept to generate an acoustic shock wave within a semiellipsoid metal disc propagated in water and then in the body so that it finally converges on a limited focal area. When the calculus (solid structure) is localized in this focal zone, it is exposed to fragmentation. According to their structure, some stones absorb the energy and become fragmented, whereas others reflect most of the energy and are more resistant to fragmentation.[95,96]

The principle of ESWL, as developed by Chaussy's group,[94-96] is to generate an acoustic shock wave (not harmful to human soft tissues), to conduct it through a water medium and then through the soft tissues, and finally to focus it on a limited focal area (Fig. 48-8). A three-dimensional targeting system allows the positioning of the shock wave generator so that the treated stone is in the focal zone. In all the more recent lithotripters, the water medium is a simple waterbag interposed between the shock wave generator and the skin, which makes the positioning of patients, particularly young children, much simpler than with the first-generation lithotripters, where the

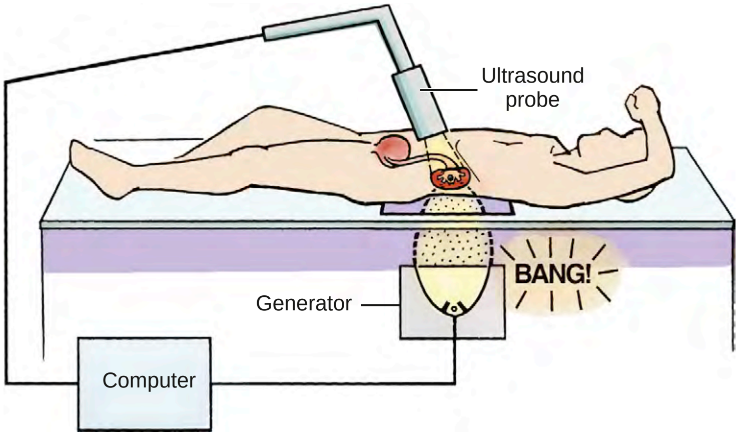

Figure 48-8 Principle of extracorporeal shock wave lithotripsy. The computer integrates the position of the stone in the three dimensions of the space, and subsequently moves the generator into the proper position. The shock wave is conducted through the water medium, then through the body, and converges on the stone.

water medium was a bath into which the patient had to be immersed (Fig. 48-9A).

The various lithotripters all are based on the same principle, but differ in the nature of the shock wave generator, the characteristics of the focal zone, the targeting system, and the anesthesia requirements. Lithotripters are either fixed or mobile. Equipment for mobile lithotripters can be shared by several treating centers.

Nature of the Shock Wave

Depending on the type of generator, the shock wave can be electrohydraulic, electroconductive, piezoelectric, or electromagnetic. Introduced in the mid-1980s, electromagnetic shock wave generators have a great energy range and can be focused precisely, theoretically delivering the most energy to the calculus with a low risk of injury to adjacent structures and with low anesthesia requirements.[97,98]

Targeting Mode

Lithotripters have targeting systems that use fluoroscopy, ultrasonography, or both modalities combined. Fluoroscopy allows the treatment of every stone, either renal or ureteral; however, an IVP or an opacification through a nephrostomy tube or ureteral catheter may be necessary for the treatment of radiolucent stones. Bush and coworkers[99] showed that the estimated radiation exposure during ESWL is less than that of diagnostic radiographic procedures (e.g., voiding cystourethrogram) or of percutaneous stone manipulation,[99] although this claim has yet to be documented in young children. Ultrasonography does not deliver x-rays, and no opacification is required for visualization of radiolucent calculi; however, ureteral stones (except the most proximal and most distal ones) cannot be localized.

Evaluation before Extracorporeal Shock Wave Lithotripsy

Before any calculus of the upper urinary tract is treated, an IVP should be performed to confirm the diagnosis (not all calcifications in the renal area are stones), to localize the calculus precisely (a stone within a calyceal diverticulum is a poor indication for ESWL), and to evaluate the permeability of the urinary tract to ensure evacuation of the fragments. A urine culture is indispensable before each treatment session; in case of asymptomatic infection, especially if associated with an infected calculus (e.g., struvite, calcium phosphate), a broad-spectrum antibiotic regimen should be administered at least for 48 hours before treatment, and an ESWL session should not be performed less than 3 weeks after an acute pyelonephritis. An evaluation of blood coagulation is also indispensable, and any coagulation disturbance should be corrected before treatment. Nontreated UTI and coagulation disturbance are

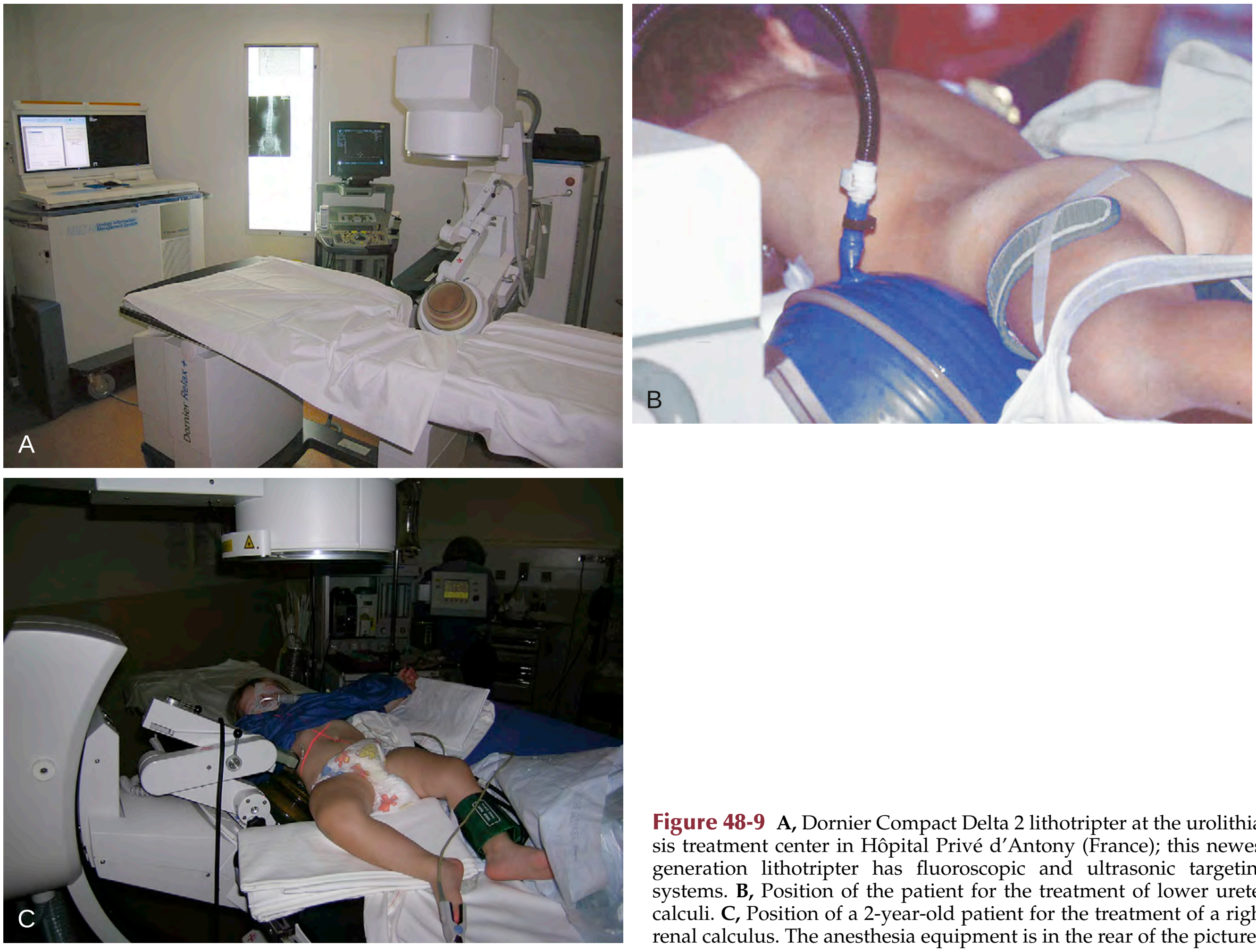

Figure 48-9 **A,** Dornier Compact Delta 2 lithotripter at the urolithiasis treatment center in Hôpital Privé d'Antony (France); this newest generation lithotripter has fluoroscopic and ultrasonic targeting systems. **B,** Position of the patient for the treatment of lower ureter calculi. **C,** Position of a 2-year-old patient for the treatment of a right renal calculus. The anesthesia equipment is in the rear of the picture.

definite contraindications to ESWL. A metabolic evaluation should be performed, particularly to detect stones that represent a poor indication for ESWL (i.e., mainly stones made of cystine, which are resistant to fragmentation).

Technique of Extracorporeal Shock Wave Lithotripsy

Positioning of the Patient

Renal and upper ureter stones are treated with the patient in supine position, and lower ureter stones are treated with the patient in prone position (see Fig. 48-9B and C). The exact positioning of the patient is an important step. Bones and gas interposition on the track of the shock wave, and fragile organs such as spleen, liver, or lung should be avoided. In small children, particularly in infants, the lung area should be protected by application on the skin above the level of the 12th rib of a thick colloidal foam. In a particular situation, such as spinal deformity, the possibilities of positioning the patient adequately for treatment should be checked before anesthesia is instituted.

Pretreatment insertion of a ureteral catheter may be necessary when the calculus creates an acute obstruction with intractable pain or pyelonephritis. The insertion of a ureteral catheter to prevent obstruction by the fragments after ESWL is more debated, particularly in young patients and infants; the ureter is more compliant than that in adults, and symptomatic Steinstrasse is unusual. Even authors who have used ureteral stenting in their preliminary experience do not routinely use stenting before ESWL, even for staghorn calculi.[100-103] We no longer use ureteral stenting, even for the treatment of large stones, in children younger than 5 years; we inform the parents that insertion of a ureteral stent or nephrostomy drain may be necessary after the session in case of symptomatic obstruction. Similar to Myers and colleagues,[103] we recommend insertion of a double-J stent in older children with large calcified stones (>25 mm in diameter) when several ESWL sessions are anticipated.

Targeting of the Stone

Targeting under fluoroscopic guidance should be performed by practitioners who are aware of dosimetry and radiation exposure limitations in pediatric patients. When ultrasonography is used, the assistance of an ultrasonographer is useful to ensure that the targeted calculus is adequately positioned in the focal zone.

Anesthesia

General anesthesia is still required in most cases for ESWL in children, at least for infants and patients younger than 6 years old, who are generally uncooperative and are upset by the atmosphere of an operating room.[100,101,103,104] At the Puigvert Foundation in Barcelona, a painless method of treatment was developed in 1987 with the Lithostar electromagnetic lithotripter (Siemens Medical). The principle is to start at low power (11 kV) and increase the power progressively so that the initial shocks desensitize the skin nerve receptors with a transcutaneous electrical nerve stimulator–like effect.[105] This method was successfully applied by Myers and others in a series of 446 pediatric patients and by several other authors.[101,103,106] There is a trend toward development of anesthesia-free ESWL with the use of piezoelectric and electromagnetic lithotripters in pediatric patients.

Stone Fragmentation

No scientific data clearly define the upper limit of power and number of shocks during an ESWL session in children. With the spark gap lithotripters, it seems that the power should be kept to less than 20 kV, and the number of shocks to a maximum of 3000 per session. The number of shocks delivered can be higher when piezoelectric or electromagnetic lithotripsy is used.[5,101-104]

The important parameters for local effects are the area of the focal zone and the maximum pressure. According to Mobley and colleagues,[98] the Siemens Lithostar has a maximum pressure of 380 bar at 19 kV with a focal zone of 11 × 90 mm. The HM3 Dornier has a maximum pressure of 340 bar at 30 kV with a focal zone of 22 × 127 mm (Dornier Medical). The total acoustic energy delivered per shock wave is less with the Lithostar than with the HM3 despite its higher maximum pressure. The Lithostar-Plus is more powerful than the Lithostar, reaching a maximum pressure of 700 bar[101]; however, because kidney tissue damage has been estimated through in vitro and animal studies to occur at pressures greater than 400 bar, the energy should probably be kept at a maximum of level 4 when using the Lithostar-Plus in children.[101,107,108] When several treatment sessions are necessary, a delay of 1 month between two sessions on the same kidney seems reasonable.

Follow-up after Treatment

KUB and ultrasound studies of the urinary tract and abdominal cavity are performed before the patient leaves the hospital, mainly to detect covert complications, such as upper tract dilation or damage to the renal parenchyma and adjacent organs. This evaluation is repeated after 1 month, together with a urine culture and, if necessary, an IVP or a CT scan. At this point, a decision is reached regarding retreatment, in case of large fragments, or follow-up, in case of small fragments or "stone-free" status. After the treatment has been completed, patients should be monitored on a yearly basis with physical examination including measurement of blood pressure, urinary tract ultrasonography, and eventual KUB films.

Complications of Extracorporeal Shock Wave Lithotripsy

A skin ecchymosis at the entry site of shock waves is the most frequent complication; it resolves spontaneously within a few days. Flank pain is unusual; when present, it resolves with the use of routine analgesic agents. Hematuria may be observed just after the session on the kidney; it is usually transitory and rarely lasts longer than 24 hours.[100,103,104] Septic complications are uncommon if the patient has sterile urine at the time of treatment; infected stones such as struvite or calcium phosphate should be treated under antibiotic prophylaxis. Few septic complications and even fewer complications requiring drainage have been reported in the literature, representing an incidence of 1% to 8% among the series (4 cases among 490 treated children). Pain and obstruction because of fragments are also uncommon in children, and even Steinstrasse when large fragments are treated is usually asymptomatic.[104]

Perinephric or subcapsular hematomas are reported in adults; they are rare and associated with uncontrolled diabetes mellitus and hypertension than with excessive parameters of treatment (i.e., kilovoltage and number of shocks).[10,109] Among 19,962 renal and ureteral calculi treated with ESWL, Mobley and colleagues[98] observed 18 major complications. There were 16 recognized perirenal hematomas (0.08%); there was one death, in a 72-year-old patient receiving heparin therapy for a prosthetic aortic valve; and one adult presented with a hemothorax that resolved with conservative therapy. Goel and coworkers[110] reported intrarenal or perirenal hematomas in 6 of 50 children after ESWL, all of which resolved spontaneously. No major renal parenchymal lesion secondary to ESWL, whatever the lithotripter used, has been reported in children. The effect of shock waves, particularly when delivered to an actively growing kidney, remains uncertain, however. Potentially, small lesions in infants could lead to a major parenchymal defect in adulthood.

In an animal study, Kaji and colleagues[111] reported no significant reduction in renal growth or renal function after ESWL. They noted a potential risk of hypertension in adulthood, with a significant increase in blood pressure in the treated animals, and several histologic changes (i.e., tubular atrophy, interstitial fibrosis, glomerular destruction, and capsular thickening). These changes were proportional to the number of shocks delivered. The shocks were not delivered to a stone, but directly to the renal parenchyma, and the energy used (26 to 29 kV) was much higher than the levels used in clinical practice. There is no doubt that extracorporeal shock waves induce some degree of parenchymal trauma. Several studies have reported an elevation of α_2-macroglobulin, a urinary marker of renal hematoma, or of tubular enzymes (e.g., creatine phosphokinase, *N*-acetyl-D-glucosaminidase); however, the variations of these markers were always transient.[112,113]

Isotopic studies have also been used to evaluate renal function and potential parenchymal damage associated with ESWL. Corbally and associates[114] performed glomerular filtration rate measurements by diethylenetriaminepentaacetic acid (DTPA) renal scans in 10 children before and 3 months after ESWL, and noted a 15% decrease in glomerular filtration rate after ESWL. This change was not statistically significant, however. Dumont and coworkers[115] noted a decrease in uptake in the treated kidney in 59% of 17 cases 48 hours after ESWL, all reversible by 6 months later. Picramenos and associates[116] observed no significant or permanent variation in relative renal uptake when comparing pretreatment values with values obtained 1 and 3 months after treatment (Dornier HM4, 18 kV) by dimercaptosuccinic acid (DMSA) in 12 children.

We used pretreatment and post-treatment DMSA renal scans to evaluate prospectively the potential functional and morphologic long-term acquired lesions after ESWL with a Sonolith 3000 (14 kV) or a Nova (14 to 20 kV) lithotripter.[34] The post-treatment scan is performed at least 6 months after the last session treatment according to the consensus identifying a renal scar as a cortical defect persisting over a 6-month period.[117] Eighty-one patients have undergone the pretreatment and post-treatment DMSA scans, including a subgroup of 42 patients younger than 2 years old at the time of treatment (mean ± SD 15 ± 6 months). In no instance could a significant variation of differential function or an acquired scar attributable to ESWL be identified even in previously scarred kidneys (Fig. 48-10).[34,118]

Thomas and coworkers[7] monitored 12 children for an average of 3 years after ESWL with a Dornier HM3 lithotripter (16 kV, average 1700 shocks), and concluded that ESWL does not significantly affect linear growth (body height) or renal function in pediatric patients. Others reported similar experience.[119,120] The possibility of development of hypertension after ESWL has been evoked through clinical and experimental studies with contradictory conclusions.[11,121,122] No study to date has proved, however, that the incidence of hypertension after ESWL related to age was higher than in the general population.

Damage induced by ESWL to adjacent organs includes hemoptysis secondary to lung contusion, which has been reported in the literature always without any serious consequences.[123,124] Thick colloidal foam is applied over the pulmonary area to prevent hemoptysis, particularly when treating upper calyx stones and in infants. Pancreatitis has been reported in adults,[125] but not in children. Hematemesis has also been observed in adults,[126] and Traxer and associates[127] reported a single episode in an 11-year-old child, with no further consequences. Mobley and colleagues[98] reported one case of small bowel perforation at the site of an adhesion from a previous appendicectomy and adjacent to a ureteral calculus. Also, thrombosis of the iliac vessels has occurred in adults after ESWL for ureteral calculi.[128,129]

These complications are described in case reports among several thousands of ESWL treatments in adults since the 1980s and have not been reported so far in pediatric patients. Although no adverse effect on audition was noted by Stoller and colleagues,[130] it is wise to shield the ears of patients (particularly infants) with a headset during treatment. Kroovand[6] documented that experimental animals exhibited no adverse effect on epiphyseal growth plates or nearby reproductive organs after ESWL, and no bone growth abnormality has been reported so far. During ESWL of distal ureteral calculi, potential damage to ovaries has been evoked. Vieweg and associates[131] specifically studied female fertility after ESWL of distal ureteral calculi and found no case of infertility. After more than 20 years of clinical applications of ESWL in children, and despite extensive clinical studies of potential side effects with careful follow-up, no serious renal or extrarenal damage imputable to extracorporeal shock waves has been observed. Also, most experimental studies in animals that have shown deleterious effects of ESWL cannot be extrapolated to clinical situations because they involved extreme parameters and conditions of treatment, far from the human practice.

Results of Extracorporeal Shock Wave Lithotripsy

Results of ESWL are particularly good in pediatric patients and, according to our experience, even better in infants.[124] These good results are probably related to the nature of the stones and to a shorter length of interposition of soft tissue between the generator and the calculus. Results of the largest and more recent series of renal and ureteral ESWL are summarized in Table 48-7.

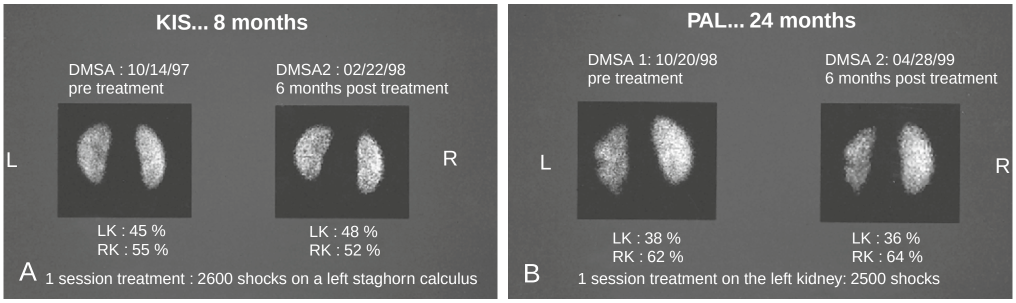

Figure 48-10 **A,** Normal pretreatment and 6-month post-treatment technetium 99m dimercaptosuccinic acid (Tc^{99m}-DMSA). **B,** Postinfectious lesions on pretreatment Tc^{99m}-DMSA; they are unchanged after extracorporeal shock wave lithotripsy.

Table 48-7 Results of Renal and Ureteral Extracorporeal Shock Wave Lithotripsy (ESWL)

Author	Lithotripter	No. Renal ESWL	No. Ureteral ESWL	% Stone-free	% Retreatment
Newman et al[93]	Dornier HM3	50	5	79	11
Sigman et al[132]	Dornier HM3	71	0	70	13
Nijman et al[133]	Dornier HM3	124	15	69	32
Myers et al[103]	Lithostar	238	208	78	9.2
Lottmann et al[144]	Sonolith Nova	78	30	79	19
Muslumanoglu et al[134]	Lithostar Plus	224	168	80	54
Netto et al[135]	Lithostar Plus	68	18	98	28
Ather and Noor[136]	Dornier MPL9000	105 (31 <5 yr)	0	95	55
Rizvi et al[137]	EDAP LT02	177	37	84	30
Landau et al[138]	Dornier HM3	0	38	97	18
Delakas et al[139]	Dornier MPL 9000X	0	25	84	25
Tan et al[140]	Lithostar	0	41	82	30
Aksoy et al[141]	Dornier MPL 9000X	0	20	75	50

A stone-free rate of around 80% is reached in most recent large series, with an average retreatment rate of 10% to 30%. Most authors consider the total absence of residual fragments as the only criterion for success because Nijman and associates[133] have shown that small residual fragments are associated with a significant recurrence rate, which in our experience is true only in the case of stones associated with a metabolic disorder. In situ ESWL for ureteral calculi yields even better results, with an average success rate greater than 80%. The new generation of lithotripters reduces the anesthesia requirement, but do not seem to improve the overall success rate and retreatment rate. Multicentric studies have lower success rates because they include centers with limited experience and poor results. Besides treating team experience, success depends on factors such as the stones and anatomic parameters, and the type of lithotripter. Stone composition and size are important predictors: Calcium oxalate dihydrate (weddellite), calcium phosphate, and struvite are easy to fragment; uric acid, calcium oxalate monohydrate (whewellite), and brushite are more resistant. Cystine stones are particularly difficult to fragment.

Stones larger than 20 mm in their largest dimension may require several treatment sessions; this is particularly true for staghorn calculi. ESWL monotherapy is not recommended for the treatment of staghorn calculi in adults; however, this may not be true in children. Orsola and associates[106] reported their experience with the treatment of 22 staghorn calculi in 15 children using a Siemens Lithostar ULTRA; there was a stone-free rate of 73.3% after an average of two ESWL sessions. Only two patients required additional surgery; no patient required a ureteral stent, and morbidity was minimal (one case of UTI that resolved with antibiotics).

We have treated 23 staghorn calculi, 6 complete and 17 partial, with a success rate of 82.6% after one to four sessions (retreatment rate of 58.8%). Only two patients required an ancillary procedure. All of the 16 infants in this series were treated with ESWL monotherapy without stenting, with a 87.5% stone-free rate and a maximum of two sessions per treatment. Two patients (8.6%) had small residual fragments.[124] The age of the patient is not a limiting factor, and infants, even with a large stone burden, are probably the best candidates for ESWL monotherapy (Fig. 48-11).The complication rate associated with renal or ureteral ESWL is very acceptable (Tables 48-8 and 48-9). Poor indications for ESWL monotherapy are large stone burden in older children; cystine stone mainly when not recent; and calculi associated with an obstructive uropathy such as UPJ, megaureter, and calculi in a calyceal diverticulum. ESWL of calculi in a long and angulated lower calyx may lead to residual fragments, and PCNL may be considered. In all other situations, ESWL should be the first-line treatment for upper urinary tract calculi.

Ureteroscopy

The principle of ureteroscopy is the retrograde introduction of an endoscope through the ureterovesical junction (UVJ) into the ureter (anterograde ureteroscopy is also feasible during a percutaneous nephroscopy, using a flexible endoscope introduced into the ureter through the UPJ). The first routine clinical applications were developed in the late 1970s by Goodmann[146] and Lyon and coworkers.[147] The first two pediatric cases were reported in 1988 by Shepherd[148] and Ritchey[149] and their colleagues in patients 4 and 7 years old. In 1997, Minevich and coworkers[150] collected 50 additional pediatric ureteroscopies from the literature. This technique is gaining popularity because most series show its efficacy and innocuousness in children. Most authors consider ureteroscopy as their first-line treatment for the management of lower ureter calculi. The limitations of this technique related to the small size of the anatomic structures have been reduced with miniaturization of the instruments. Two difficulties persist: first, to achieve adequate experience, considering the limited number of indications (two to five patients treated per year in most series), and second, the availability of the equipment.

Technique

Most ureteroscopies in children are performed with the patient under general anesthesia. Urine must be sterile at the time of the procedure, and perioperative antibiotic prophylaxis is a safe option because extravasation of urine may occur. The patient is placed in the lithotomy position, and the stone is located with fluoroscopy. It is crucial that all of the potentially needed instruments are available, ready, and operational before the procedure begins; also, informed consent must be obtained from the parents to change the strategy (including performing an open procedure) in case of failure.

Ureteroscopes

Rigid and flexible ureteroscopes are available. Technologic improvements in rigid ureteroscopes have led to progressive reduction in caliber of the sheath size, while maintaining a working channel as large as possible to allow the introduction of forceps, stents, baskets, and lithotripsy probes. The Circon 6.9 ACMI rigid miniscope (Circon Corp, Portland, OR) has a 5F working channel. The 4.8F Wolf ureteroscope has a working channel that can accommodate only electrohydraulic lithotripsy (EHL) or laser lithotripsy probes. Flexible ureteroscopes are also available, although the size of the working channel is small and cannot accommodate rigid tools.

Access to the Stone

Dilation of the Ureterovesical Junction

If the ureter, particularly in children, is easily distensible, the UVJ and intramural portion of the ureter represent a relatively narrow segment that may not easily accommodate the ureteroscope. The need for dilation of this segment depends on the size of the ureter and the size of the instruments. When dilation is required, it can be done acutely, performed at the initial phase of the procedure. Acute dilation consists of the introduction through the UVJ of catheters of increasing size, bougies with olivary tips, or inflatable balloon dilating catheters. Dilation should always be kept at the minimal caliber that allows introduction of the ureteroscope. Excessive acute dilation carries the risk of damage to the UVJ that would create a postoperative vesicoureteral reflux or stricture.

Subacute dilation, although it is a two-stage procedure, is probably less aggressive. It consists of the introduction of a ureteral catheter or a double-J stent a few days before the ureteroscopy. Great care must be taken during these maneuvers not to dislodge the stone, which might migrate up to the kidney. Although some authors still advocate UVJ dilation,[49] more and more consider that in pediatric patients UVJ dilation is not required when using small instruments.[151] These authors, similar to Scarpa and associates,[152] prefer to choose the instruments and methods best adapted to the kind of treated ureter, rather than adapting the ureter to the available instrument.

Placement of a Guidewire

Placement of a guidewire up to the renal cavities is the next step of the procedure; it helps the progression of the ureteroscope by "showing the right way" (Fig. 48-12A); also, in case of perforation, bleeding, or any problem during the procedure, it is a safety guard that allows the insertion of a ureteral catheter. In the absence of such a guidewire, when a complication such as a false route or perforation occurs, the insertion of a ureteral catheter may be impossible, and the situation becomes critical.

Introduction of the Ureteroscope

The ureteroscope is introduced into the urethral meatus and progresses under direct vision, following the guidewire. In boys, great care must be taken during the entire procedure not to create an injury to the fragile urethral mucosa with the subsequent risk of secondary urethral stenosis. When reaching the ureteral meatus, a rotation of the instrument usually facilitates its introduction into the UVJ. Active hydrodistention also assists in the introduction of the ureteroscope.[151] Still following the guidewire, the progression is conducted along the ureteral lumen, strictly avoiding any blind or traumatic

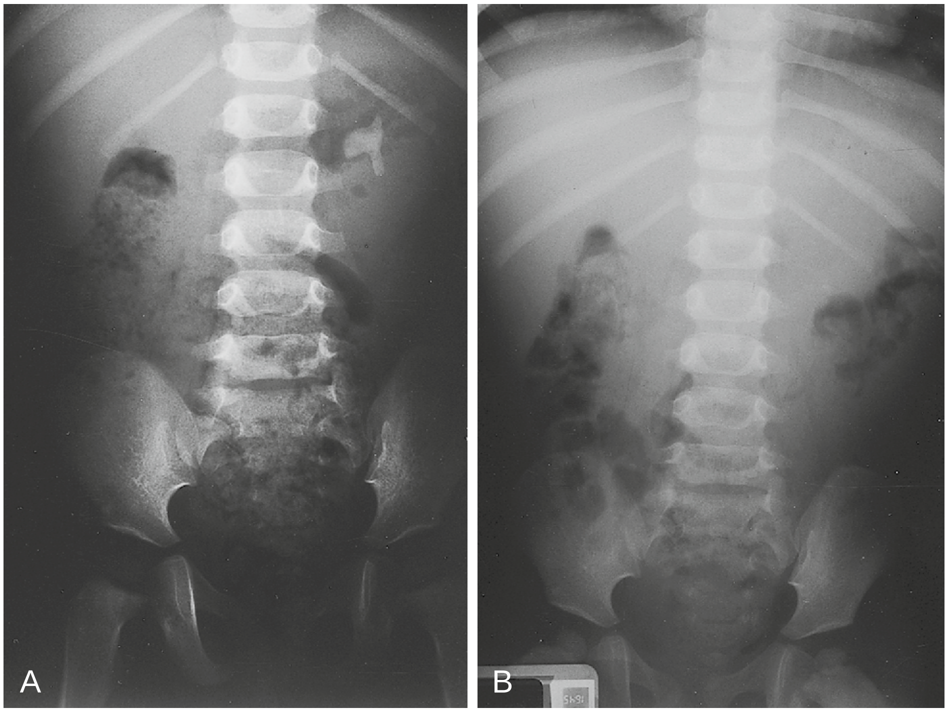

Figure 48-11 **A,** Staghorn calculus of the left kidney in a 20-month-old boy. **B,** Small fragments are visible 48 hours after extracorporeal shock wave lithotripsy (ESWL). The patient was stone-free 1 month after a single treatment session.

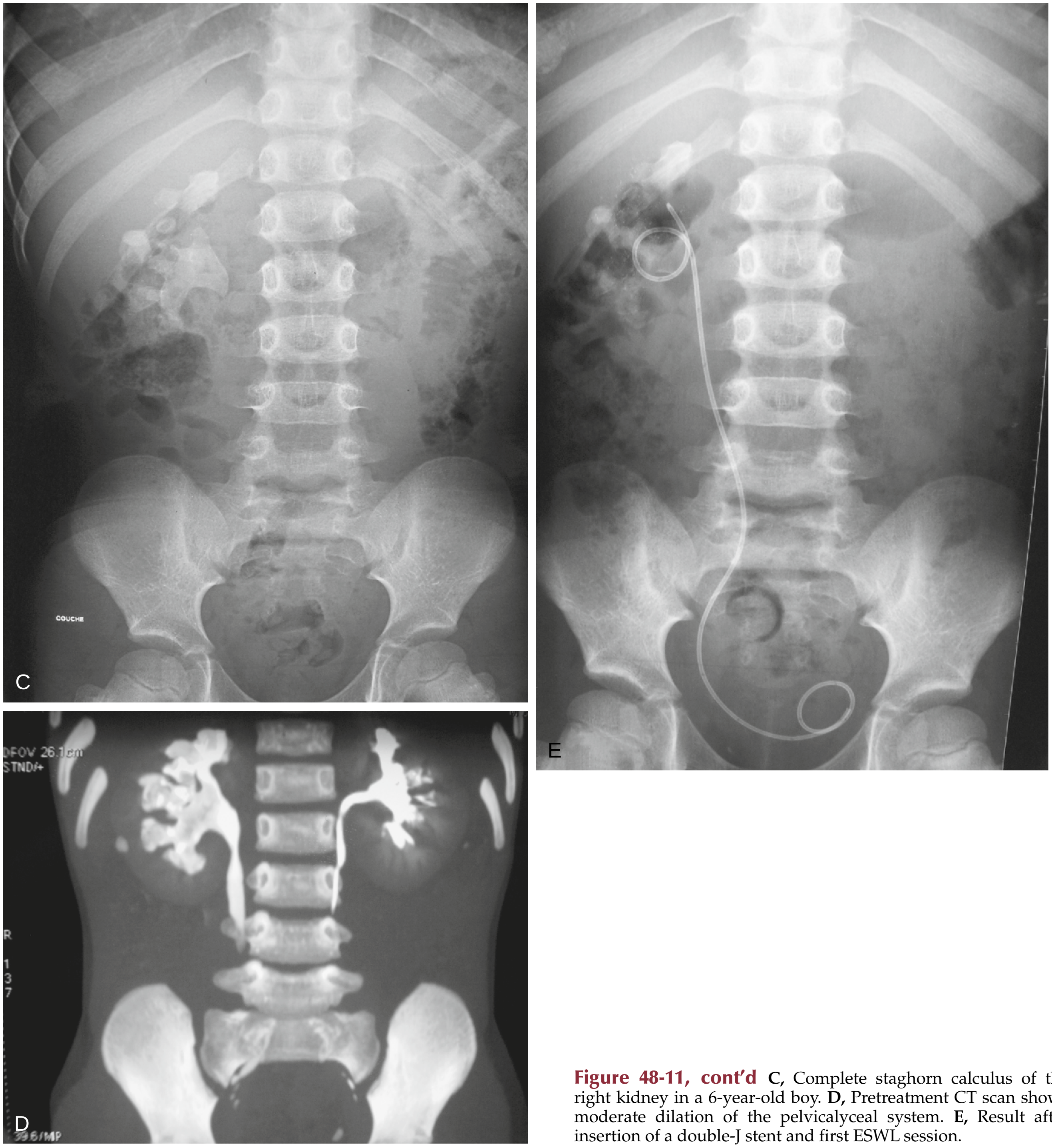

Figure 48-11, cont'd **C,** Complete staghorn calculus of the right kidney in a 6-year-old boy. **D,** Pretreatment CT scan shows moderate dilation of the pelvicalyceal system. **E,** Result after insertion of a double-J stent and first ESWL session.

maneuver. Fluoroscopy may be useful to monitor the progression of the instrument, eventually associated with the injection of diluted contrast medium (Fig. 48-12B). As soon as the stone is reached, the progression stops, and the management of the calculus per se can begin. The progression of a flexible ureteroscope is conducted either under direct vision or, preferably, with the use of a guidewire previously introduced into the working channel. The progression of the instrument is monitored under fluoroscopy with or without the use of contrast medium.

Management of the Stone

The stone can be extracted intact or be fragmented first with secondary extraction of the fragments. In stone extraction with a Dormia basket catheter, only stones that are of small size and free in the ureteral lumen with no connection to the mucosa can be extracted without a previous lithotripsy. Several Dormia catheters are available depending on the number (three to six) and shape of the spiral wires composing the basket and on the size of the catheter (1.7F to 4.7F). The procedure

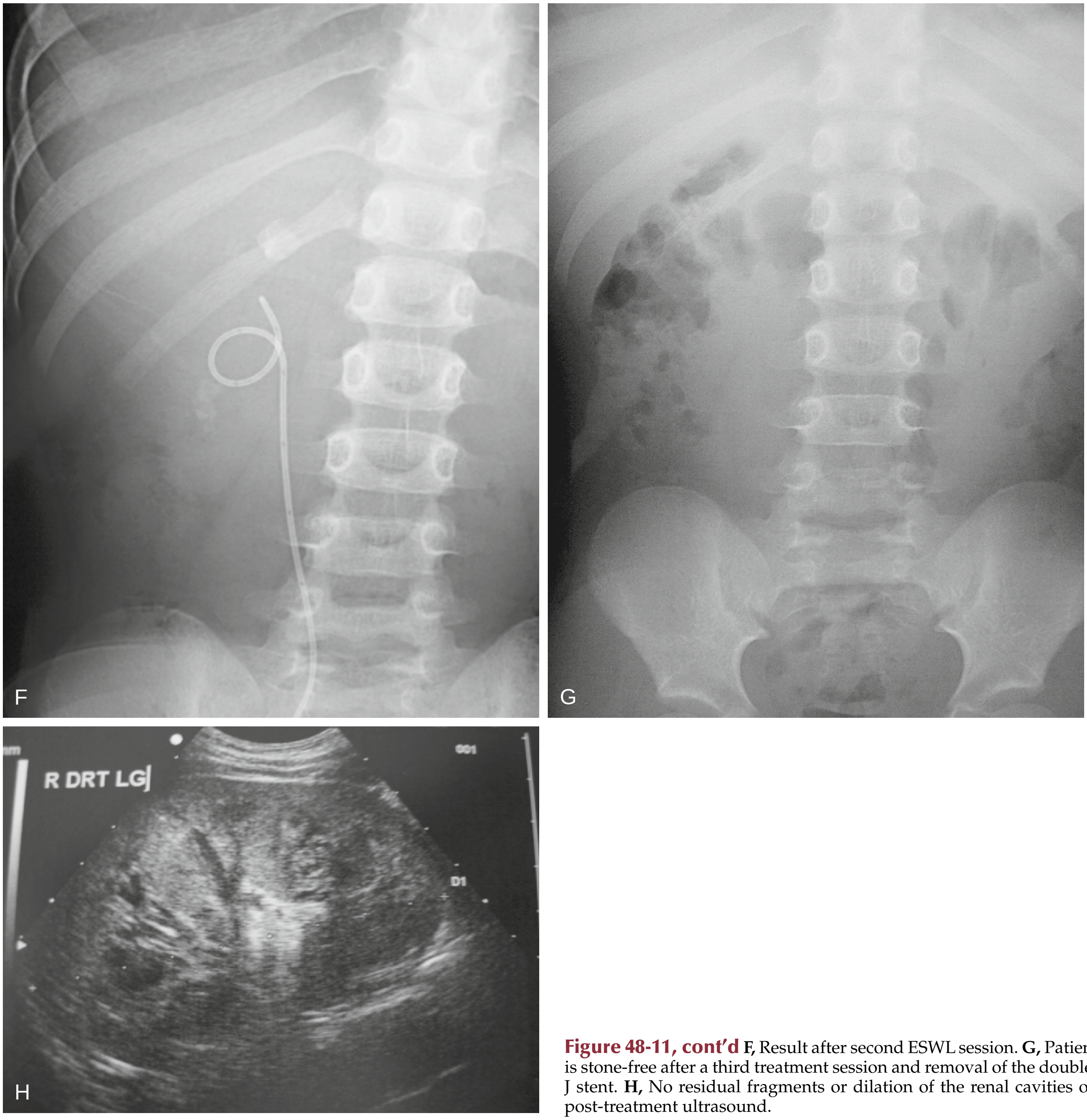

Figure 48-11, cont'd **F,** Result after second ESWL session. **G,** Patient is stone-free after a third treatment session and removal of the double-J stent. **H,** No residual fragments or dilation of the renal cavities on post-treatment ultrasound.

must be performed under vision control: The catheter is introduced into the working channel of the ureteroscope until the tip becomes visible close to the stone level; the assistant then opens the basket, and the operator, with a rotation of the catheter, introduces the stone into the basket. The assistant then closes the basket sufficiently to trap the stone within it. The operator checks that the basket is free in the ureteral lumen, and in particular that no ureteral mucosa has been trapped within the branches of the basket. The withdrawal of the ureteroscope and the basket can then start safely.

The basket with the stone in it must be kept under vision control until the extraction out of the urinary tract is completed. A critical phase is the extraction of the basket out of the UVJ; at this level, a stone that is too large for direct extraction can be stopped in its progression. The traction exerted on the basket catheter must always be gentle. If the stone is encrusted in the ureteral mucosa or is too large to be extracted directly through the UVJ, a lithotripsy is required. Excessive traction on the basket catheter can lead to a ureteral avulsion, which is a major complication.

LITHOTRIPSY

Fragmentation can be performed by several means: ultrasonic lithotripsy, EHL, laser lithotripsy, and ballistic lithotripsy. Ultrasonic lithotripsy consists of the transmission of high-frequency vibrations along a rigid metal probe from the

Table 48-8 Complications of Renal Lithotripsy

Author	No. Patients	Complications	Ancillary Procedures	Complication Rate (%)
Afshar et al[142]	83	Renal colic: 6	Double-J stent: 2	10.84
		Gross hematuria: 3	Ureteroscopy: 3	
Muslumanoglu et al[134]	344	Steinstrasse: 13 (7.8%)	In situ ESWL: 8	9.6
		Hydronephrosis: 14 (4%)	Double-J stent: 14	
		UTI: 4 (1.2%)		
		Renal colic: 10 (2.9%)		
Al-Busaidi et al[143]	42	Steinstrasse + sepsis: 2	Nephrostomy + ureteroscopy	10
		Partial obstruction: 2	Ureteroscopy: 1	
			In situ ESWL: 1	
Netto et al[135]	86	Renal colic: 8	None	10
Ather and Noor[136]	105	Renal colic: 3 (3%)	EHL/holmium:YAG laser/basket	8
		Steinstrasse: 2 (2%)		
		Febrile UTI: 3 (3%)		
Rizvi et al[137]	177	Renal colic: 18 (10%)	None	19
		Fever: 15 (8.5%)	None	
		Steinstrasse: 2 (1.1%)	Nephrostomy: 2	
Aksoy et al[141]	129	Steinstrasse: 7 (7.8%)	Ureteroscopy: 2	14
		UTI: 10 (7.75%)	None	
		Subcapsular hematoma: 1	None	
Lottmann et al[144]	23 staghorn	Upper ureteral: 1 obstruction	Pyelotomy: 1	4
Orsola et al[106]	15 staghorn	Febrile UTI: 1	None	6.6

EHL, electrohydraulic lithotripsy; ESWL, extracorporeal shock wave lithotripsy; UTI, urinary tract infection.

Table 48-9 Complications of Ureteral Extracorporeal Shock Wave Lithotripsy

Author	No. Patients	Complications	Ancillary Procedures	Complication Rate (%)
Delakas et al[139]	25	Renal colic: 6 (24%)	None	24
Landau et al[138]	38	None	None	0
Tan et al[140]	41	Renal colic: 3 (7.9%)	None	7.9
Gofrit et al[145]	38	UTI: 1	None	7.8
		Renal colic: 1		
		Laryngospasm: 1		

UTI, urinary tract infection.

source to the stone. Fragmentation occurs at the level where the tip of the metal transducer is in contact with the stone. Ultrasonic lithotripsy requires a rigid ureteroscope; the stone must be secured within a Dormia basket to prevent upward migration during fragmentation. The temperature increases along the metallic probe during the procedure, resulting in a risk of thermal injury to the ureteral mucosa. A hollow central core allows suction of small fragments and irrigation through the transducer during the procedure, cooling the system. The size of this lumen is reduced, however, and it is difficult to maintain its patency during the disintegration process.

EHL consists of a coaxial flexible probe (1.6F to 5F) connected to a shock wave generator. EHL is associated with a high risk of damage to the ureteral mucosa and a high incidence of perforation, particularly when the calculus is embedded in the ureteral mucosa. EHL should be avoided for ureterolithotripsy.

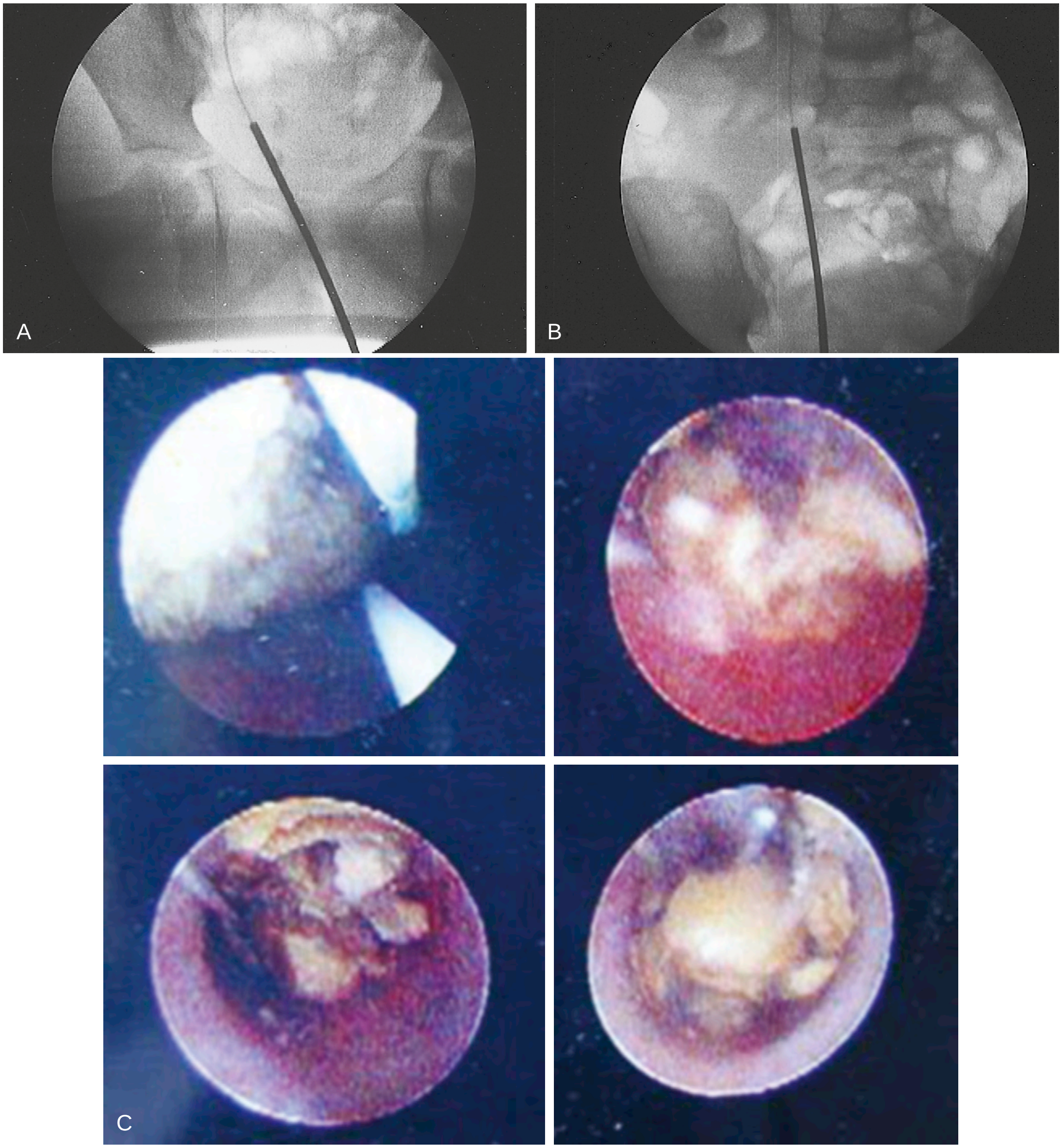

Figure 48-12 **A,** Ureteroscopy in a 3-year-old girl shows insertion of the guidewire. **B,** Insertion of an 8F ureteroscope up to the lumbar ureter. **C,** Ballistic lithotripsy with a 3F probe of the Swiss Lithoclast.

Laser lithotripsy is particularly well adapted to pediatric ureterolithotripsy because of the limited size (250 to 320 μm) and the flexibility of the optic fibers used to deliver the energy. Two different laser sources are currently used for lithotripsy: the pulsed-dye laser and the holmium:yttrium-aluminum-garnet (YAG) laser. The pulsed-dye laser generates an acoustic shock wave that acts like a hammer to fragment the stone. There is no risk for the adjacent soft tissue, but everyone present in the room must wear protective glasses because accidental eye exposure to the laser beam can create irreversible damage to the retina. The holmium:YAG laser is also a pulsed laser that acts via a thermal effect. It is particularly effective on cystine stones and produces smaller fragments than pulsed-dye lasers do.[153,154] There is no risk of ocular lesion in case of an accidental exposure. Because of the thermal effect, however, there is a risk of thermal injury to the adjacent ureteral wall and to guidewires.[155]

Ballistic lithotripsy is based on a pure mechanical hammer effect transmitted along an 0.8-mm probe that requires a rigid straight ureteroscope with a 3F minimum working channel.[156] Any incurvature of the probe should be avoided because it reduces the amount of energy transmitted (see Fig. 48-12C). Ballistic lithotripsy is safe for the adjacent soft tissues.

Extraction of the Fragments

After lithotripsy, the fragments are extracted with the use of a Dormia basket or a grasping forceps. Small fragments (<2 mm) are practically impossible to trap and should be left in place rather than prolonging unnecessarily the potentially traumatic endoscopic procedures.

Postoperative Ureteral Stenting

In case of acute dilation of the UVJ, if the procedure has been long with eventual trauma to the mucosa, if a perforation has occurred, and routinely for most authors, it is recommended to leave a ureteral catheter in place to prevent postoperative pain related to edema, upper urinary tract obstruction, or a retroperitoneal urinoma. Depending on the local situation and the experience of the operator, a ureteral catheter is inserted for 24 to 48 hours, or a double-J stent is inserted for a longer period. A double-J stent with an attached string can be removed without additional anesthesia.

Complications of Ureteroscopy

During the various steps of the procedure, complications of various degrees of severity may occur. The first may be the impossibility of inserting a guidewire above the level of an impacted calculus; performing a ureteroscopy without a guidewire is hazardous and probably should not be attempted if the operator is not well experienced. If the procedure is pursued, a guidewire should be inserted whenever possible. The second potential complication is the impossibility of introducing the ureteroscope through the UVJ despite an acute dilation because a perforation has occurred in the intramural ureter during the preliminary maneuvers. Several options can be discussed in this situation depending on the context: a straightforward open ureterolithotomy; ESWL; or leaving a double-J stent in place for a few days to provide a subacute dilation of the UVJ, with a second attempt performed after this delay.

During the preliminary maneuvers, during the progression of the ureteroscope under hydrodilation, or during the lithotripsy, the calculus can be dislodged from its position and flushed upward. The new position of the stone can be assessed with fluoroscopy and eventual injection of contrast medium. In some instances, it is possible to progress further upward, catch the stone in a basket, and proceed to lithotripsy. In other cases, it becomes impossible to progress further with the ureteroscope without significant risk for the urethra (in boys), the UVJ, or the ureter in general; it is then safer to flush the stone back to the kidney if it is not already there, leave a catheter large enough to prevent secondary migration back down the ureter, and perform in a second step an ESWL or a percutaneous stone extraction. During the basket maneuvers, the basket can get blocked with ureteral folds trapped within the wires; if the basket cannot be reopened, the procedure must be converted to open surgery.

A perforation of the ureteral wall may occur during lithotripsy, with encrusted stones when using EHL; the stone can eventually be expulsed outside the ureteral lumen. Injection of contrast medium confirms the diagnosis. These perforations are usually without consequences, provided that a guidewire has been inserted at the initial phase of the procedure, allowing the safe insertion of a ureteral catheter, which is left in place for a few days until the retroperitoneal urinoma has been reabsorbed, and the ureteral perforation has healed. A calculus expulsed in the retroperitoneal space can be ignored without further consequences; the patient or parents should be informed that the stone, which may still be seen on radiographs, does not need further investigation because it is outside the urinary tract.

The most severe complication that may occur during ureteroscopy is ureteral avulsion secondary to traumatic maneuvers, particularly excessive traction on a Dormia basket to remove a stone that is too large or encrusted. The ureteral avulsion must be recognized during the procedure by contrast medium injection under fluoroscopic control, and it necessitates an open surgery repair.

A vesicoureteral reflux may occur, particularly after acute dilation of the UVJ. The true incidence of vesicoureteral reflux is unknown, but seems to be limited: Minevich and coworkers[150] mentioned that 3 of 52 patients in published reports showed reflux. These refluxes seem to be transitory and without clinical consequences, and the opinion of most authors is that a voiding cystourethrogram should be performed only in patients with a postoperative upper tract dilation or symptomatic UTI.[49,157] The occurrence of ureteral strictures also seems to be low—1 case among 52 procedures using 7.2F to 11F ureteroscopes from the review of the literature by Minevich and coworkers[150]—and underlines the need to avoid traumatic ureteroscopy. Thomas and colleagues[7] performed renal quantitative scintiscan studies with iodine 133–hippurate in 10 patients after ureteroscopy, and showed adequate growth and function in the treated kidneys without evidence of obstruction.

Results of Ureterolithotripsy in Pediatric Patients

Since the first two case reports in 1988 by Shepherd[148] and Ritchey[149] and their colleagues, several series have been published in the literature arguing for the feasibility, efficacy, and safety of ureterolithotripsy in children (Table 48-10). All these series report a high success rate without any serious complications. Among 66 children (2 to 15 years old), Bassiri and colleagues[159] reported 3 failures and stone that moved to the kidney in 4. In the remaining 59 children, the complication rate was 23%: renal colic (1), gross hematuria (11), and pyelonephritis (3). Among 35 children (1 to 14 years old), Dogan and associates[162] reported 2 stones pushed back in the kidney, and 2 ureteral perforations.

Percutaneous Nephrolithotripsy

The principle of PCNL is the percutaneous introduction of an endoscope into the pelvicalyceal cavities; through this access, the stone is reached, identified, and fragmented when necessary, and then the stone or its fragments are extracted through the same percutaneous channel. Feinström and Johannson in 1976[165] were the first to report a percutaneous stone extraction. After the first description of the concept in adult patients, it took almost 10 years before the first reports concerning pediatric PCNL were published, by Woodside and associates in 1985[166] and Papanicolaou and colleagues in 1986.[167] The advent of ESWL during the same period has limited the expansion of this more invasive technique of stone removal. PCNL has its place for the treatment of renal stones in children, however, mainly when ESWL is contraindicated or has failed.

Technical Aspects of Percutaneous Nephrolithotripsy

The first step in PCNL is to create an access from the skin to the desired calyx. The tract is dilated sufficiently to introduce the endoscope, and the stone is visualized and either extracted directly or fragmented first and the fragments secondarily removed. The endoscope is retrieved and almost systematically replaced by a nephrostomy tube. In children, the procedure is usually performed with the patient under general anesthesia.

Table 48-10 Results of Ureterolithotripsy in Pediatric Patients

Author	No. Patients	Patient Age	Procedure Ureteroscope	Procedure Lithotripsy	Stone-free Rate (%)
Thomas et al[204]	16	16 mo–15 yr	7.5F/8.5F/11.5F	EHL	100
Scarpa et al[152]	7	3.5-10 yr	4.8F/7F	Pulsed dye laser ballistic	100
Kurzrock et al[205]	17	10 mo–16 yr	6.9F/7F	Pulsed dye laser	100
Minevich et al[150]	7	7-16 yr	6.9F/7F/9.5F	EHL	85
Jayanthi et al[157]	12	2-14 yr	7.5F/8F/9.5F	EHL/holmium:YAG laser	92
Bassiri et al[159]	66	2-15 yr	8F/11.5F	EHL or pneumatic/basket	88
Al-Busaidi et al[160]	26	2-12 yr	8F	Holmium:YAG	92
Holman et al[161]	30	8 mo–14 yr	9.5F	Not mentioned	90
Dogan et al[162]	33	1-14 yr	7.5F/8F/10F	Holmium:YAG or pneumatic/grasper	82
Tan et al[163]	21	2-14 yr	7.5F/8F/9.5F	EHL/holmium:YAG laser/basket	95
Satar et al[164]	33	9 mo–15 yr	6.9F/10F	Pneumatic lithotripsy/forceps	94

EHL, electrohydraulic lithotripsy.

The patient is settled in a ventral position. All the necessary material for access into the collecting system, lithotripsy, removal of the stone or fragments, fluoroscopy, and ultrasonography should be available before the procedure starts. Also, any UTI must be treated by appropriate antibiotics.

Creation of the Nephrostomy Tract

A needle (usually 18 to 22 gauge) is introduced along the posterior axillary line (a line is drawn from the external extremity of the acromion to the posterior superior iliac spine) into the appropriate calyx (Fig. 48-13). This introduction can be done under fluoroscopic control or under ultrasound guidance (Fig. 48-14A-D); the latter is more appropriate to aim the calculus and enter the kidney along a posterolateral axis in a relatively avascular area of the kidney where the parenchyma is thin. The appropriate calyx is penetrated through the papilla. Ultrasound guidance also reduces the irradiation of the patient. When the renal cavities are not dilated, it is useful to insert a ureteral catheter and inject either saline or contrast medium to dilate the cavities and improve their visualization. As soon as the needle has been inserted in the pelvicalyceal system, an injection of contrast medium and fluoroscopic control allow the physician to check its appropriate position. If the needle is in a calyx adjacent to the one containing the stone, it should be removed, and a new puncture should be performed.

Dilation of the Nephrostomy Tract

A guidewire is introduced into the needle and ideally is pushed through the UPJ down the ureter (Fig. 48-14E). This allows an adequate dilation of the tract without risk of perforating the pelvis with the dilators. Various types of dilators can be used to dilate the nephrostomy tract, but the principle is always to limit the dilation to the caliber of the nephroscope and its sheath. Another principle is that the level of dilation and the size of the nephroscope should be adapted to the age of the patient, the size of the kidney, and the degree of dilation of the pelvicalyceal system. The range of tract dilation is from 11F to 24F and more. In early reported series, authors dilated the tract up to 26F in patients 5 to 16 years old; however, in 1984, Clayman and associates[168] claimed that it seemed advantageous to limit dilation to the minimum size necessary for efficient stone removal.

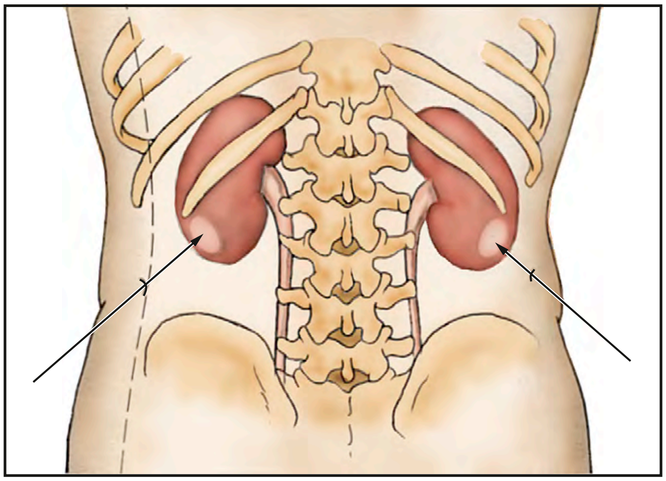

Figure 48-13 Puncture of the calyx along the posterior axillary line. (From Le Duc A, Teillac P, Cussenot O, et al. Chirurgie percutanée du rein pour lithiase. Paris: Techniques Chirurgicales Urologie; 1994:No. 41090 B. Editions Scientifiques et Medicales Elsevier SAS. Tout droits reservés.)

The less invasive percutaneous access to the pelvicalyceal cavities is described by Jackman and coworkers[169] as the "mini-perc" technique: a 0.035-inch floppy-tipped guidewire is inserted through the access needle and kept as a safety wire; a stiffer working wire is then introduced. The fascia is incised, and an 11F peel-away vascular access sheath with its trocar is introduced along the guidewire into the pelvicalyceal system under fluoroscopic control. No dilation is needed before this maneuver. The trocar is removed, and a 7F rigid pediatric cystoscope or a 9.5F flexible ureteroscope is inserted through the peel-away sheath. Among the advantages listed by the authors of this "mini-perc" method are the universal availability of the introducer sets and the avoidance of excessive dilation, which reduces the trauma of tract dilation and tract pain. Also, the cost of the kit is much lower than the price of sequential or balloon dilator sets.

INTRODUCTION OF THE INSTRUMENT

After the tract has been dilated, the instrument can be introduced during the same session (Fig. 48-14F). In some instances, owing to bleeding or routinely for some authors, a nephrostomy tube is left in place for 48 hours, after which the patient is brought back to the operating room for completion of the procedure. Also, in the case of severe sepsis associated with an obstructing calculus, a nephrostomy tube is inserted, and the infection is treated before a safe percutaneous tract dilation can be performed. The insertion of a working sheath of a size slightly superior to that of the endoscope helps to maintain the tract opened to the pelvicalyceal system, avoids fluid leakage in the renal fossa, and increases the safety of the procedure.

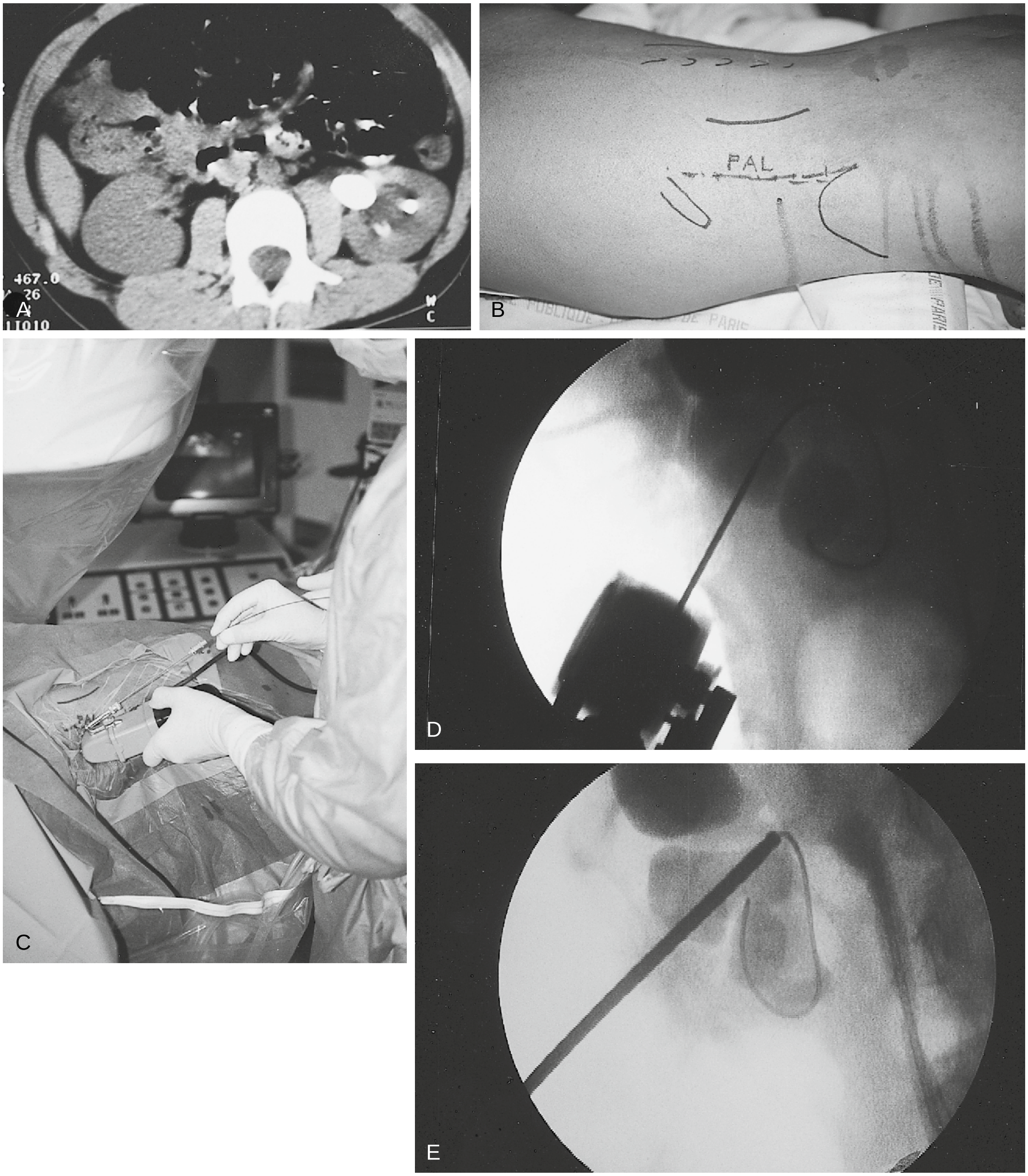

Figure 48-14 **A,** Non–contrast-enhanced CT scan of a cystine staghorn calculus in a 12-year-old boy. **B,** Posterior axillary line. **C,** Puncture of the cavities under ultrasound guidance. **D,** Puncture assisted with fluoroscopic guidance. **E,** Dilation of the puncture tract.

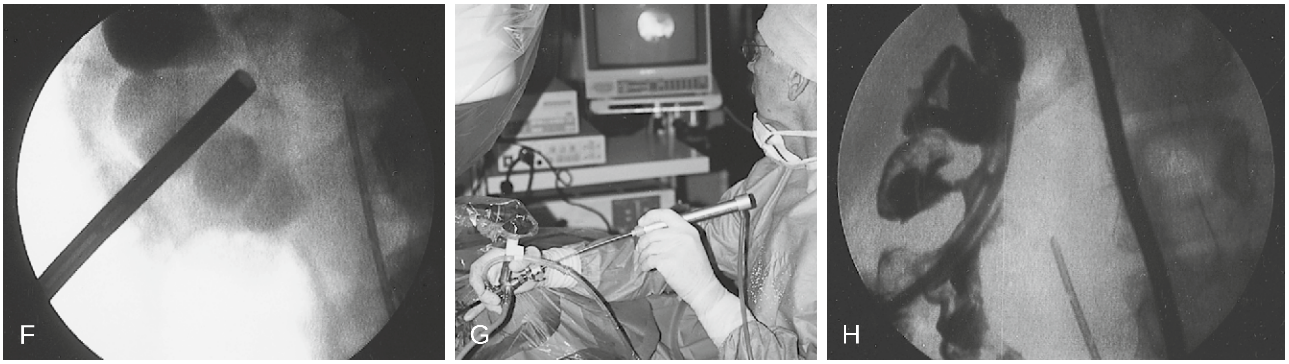

Figure 48-14, cont'd **F,** Insertion of the nephroscope. **G,** Ballistic lithotripsy using the Swiss Lithoclast. **H,** Insertion of a nephrostomy tube at the end of the procedure.

Stone Destruction and Extraction

When the stone is identified, it can eventually be extracted intact with the use of a grasping forceps. If the size of the stone is such that it cannot be extracted directly, it must be fragmented first by ultrasonic lithotripsy, EHL, ballistic lithotripsy, or laser tripsy, as previously described.

Ballistic lithotripsy (Swiss lithoclast) is very effective and safe for the surrounding soft tissues. Desai and associates[170] have developed an 0.8-mm probe with a 7F section cannula that can be introduced in the working channel of a 14F pediatric nephroscope (Fig. 48-14G).

The holmium:YAG laser is, as claimed by Teichman and coworkers,[171] an effective tool able to fragment any stone into pieces smaller than 1 mm. The 200-μm to 1000-μm laser optic fibers can be inserted in the working channels of the smallest rigid or flexible endoscopes, but inadvertent exposure of the urinary tract to the laser beam may lead to perforation or bleeding, and the procedure must be conducted under careful visual control.

When lithotripsy is completed, fragments are either aspirated through a cannula or extracted with grasping forceps. In the case of a large stone burden extended into several calyces, it may be impossible to perform a complete stone fragmentation and extraction through a single percutaneous tract. One or several more accesses may be necessary. Depending on the composition of the stone, the local condition, and the choice and experience of the operator, a long, fastidious procedure in eventually multiple sessions may balanced against other combined therapeutic alternatives such as ESWL.

Postoperative Drainage

The pelvicalyceal system is controlled under fluoroscopy with eventual injection of contrast medium to check the patency of the ureter and to rule out a perforation of the pelvis. A nephrostomy tube is left in the tract. A radiologic study is usually performed after 48 hours, and if the patient is stone-free, and the urinary tract is intact and patent down to the bladder, the nephrostomy tube is removed. If residual fragments are still present (sometimes the procedure has to be interrupted before complete stone extraction because of excessive bleeding or excessive duration), in the pelvicalyceal system or in the ureter, a second session is performed, or, if the fragments are small, the nephrostomy tube is kept in place until they are eliminated.

Complications Associated with Percutaneous Nephrolithotripsy

PCNL is an invasive procedure, and severe complications may occur during each phase of the procedure. Blood loss requiring transfusion and sepsis are the main significant potential complications. The risk of hemorrhage is increased in pediatric patients compared with adults because the small size of the kidney and pelvicalyceal system may be inadequate for the caliber of the instruments. High blood pressure, bleeding disorders, and uncontrolled sepsis are contraindications for the procedure.

During the creation of the nephrostomy tract, perforation of adjacent structures and significant hemorrhage may occur. Perforation of adjacent structures has been described, with the pleura and the colon being most at risk. Perforation of the pleura usually occurs during access to the upper pole and may lead to a pneumothorax or hemothorax, which may require insertion of a pleural drain. A colonic perforation must be recognized; it may be treated conservatively by leaving a drain in the tract for a few days, but may require an open surgical repair. Perforation of the duodenum, liver, or spleen also theoretically may occur, although such complications have not been reported so far in children. This possibility underlines the need for careful monitoring under ultrasonic control of the tract of puncture during percutaneous access to the kidney.

Bleeding and vascular injury are mainly related to an inadequate puncture tract or to an excessive dilation. Bleeding is generally of venous origin and can be controlled in most cases by the insertion of a tube in the nephrostomy tract; the tube is clamped for several minutes to allow clot formation in the pelvicalyceal system, and the tube compresses the bleeding vessels along the tract. Significant bleeding usually necessitates interruption of the procedure until after a few days when the tract is organized. Arterial injury has been reported in adults; it may induce a severe hemorrhage and require immediate arteriography to confirm the diagnosis, identify the bleeding artery, and perform an embolization.

During the phase of lithotripsy, in addition to the risk of significant blood loss, bleeding carries the risk of intravascular extravasation, which might induce a dangerous fluid overload in a young child. Fluid infusion should be carefully monitored throughout the procedure, which should be interrupted if there is prolonged venous bleeding, or if injection of contrast medium shows intravascular extravasation. In 1989, Zattoni and colleagues[172] observed that the creation of the nephrostomy tract and its dilation seemed to be responsible for most renal vascular complications. Significant bleeding was reported by Callaway and colleagues[173] in 4 of 18 children treated with PCNL; 3 of them required a blood transfusion, and the procedure was interrupted in the fourth patient, who required a delayed second stage. Tuncay and associates[174] reported major bleeding requiring transfusion in 3 of 12 PCNL procedures. They dilated the tract from 24F in children younger than 8 years old up to 30F in older children. Desai and associates,[175] in a large series of 40 patients younger than 15 years old, observed that blood loss was proportional to the level of dilation of the tract rather than the number of access tracts. No major bleeding was reported by the authors using the "mini-perc" technique.[169]

Lesions of the urinary tract (e.g., perforation of the pelvis) may also occur, leading to a retroperitoneal extravasation of fluid, which must be recognized (the kidney appears to float in the renal fossa) because it may lead to a fluid overload. Pugach and coworkers[176] reported a case of massive hydrothorax and hydro-abdomen complicating PCNL in a child. This perforation is best prevented during the dilation phase by inserting the dilators on a guidewire descending into the ureter, and by not inserting the dilators too far into the pelvicalyceal system. During the lithotripsy phase, constant visual control is needed, mainly when using EHL or the holmium:YAG laser. Most urinary tract lesions can be treated conservatively.[177] Jayanthi and colleagues,[157] using a 24F nephroscope, induced a complete disruption of the proximal ureter requiring a salvage ureterocalycostomy. The use of smaller instruments should reduce the incidence of iatrogenic injury to the kidney and pelvicalyceal system. Children are particularly sensitive to hypothermia, and PCNL may be prolonged; this is why all the irrigants should be warmed adequately, and the patient's body core temperature should be carefully monitored throughout the procedure.

Sepsis is another potential complication associated with PCNL. A moderate increase in temperature caused by focal parenchymal necrosis along the puncture tract is usual and has no consequences; severe sepsis may be observed mainly in patients with infected (struvite or calcium phosphate) stones.[176,177] UTI must be controlled before the PCNL procedure is performed.

In the long-term, the degree of kidney damage induced by PCNL has been shown in animal studies and in clinical studies of adult patients to be moderate. Mor and colleagues[177] performed a pretreatment and post-treatment DMSA or mercaptoacetyltriglycine (MAG3) renal scan in 10 patients; no change in differential function or scar was observed except in 1 patient who had long-standing stone disease complicated by recurrent UTI that necessitated three PCNL procedures in 4 years.

Results of Percutaneous Nephrolithotripsy in Children

Results and complications of PCNL in children are summarized on Tables 48-11 and 48-12.

Open Surgical Stone Extraction

Open surgical stone extraction is indicated in the rare eventuality when the indications for ESWL and minimally invasive techniques are poor, or these modalities have failed. More frequent is the situation of a calculus that has developed above an obstructive uropathy, such as UPJ obstruction, megaureter, or ureterocele (Fig. 48-15). Treatment must address the relief of obstruction and extraction of the stone, usually by an open procedure. A total or partial nephrectomy may also be required in cases of extensive parenchymal damage.

Renal Calculi

An anterior approach, such as that described by Duckett and colleagues,[186] usually provides a satisfactory exposure of the entire kidney in children. In adolescents or obese children, a flank incision may be a better option, particularly when access to the upper pole is needed; 12th rib resection usually is unnecessary. The procedures are performed extraperitoneally. In a reoperation, a transperitoneal approach may be preferable, however, to carry the dissection through unoperated tissues and to avoid an inadvertent injury to intraperitoneal structures.

When the calculus and associated obstruction and infection have induced extensive parenchymal damage with a residual function of the involved kidney less than 10% of the total renal function, a nephrectomy is indicated. A partial nephrectomy is indicated in children with impacted calculi and severe parenchymal atrophy.[33] For calculus removal, a pyelotomy is the least invasive route; the pelvic incision should have a U shape distant to the UPJ and can be prolonged when needed along the calyceal infundibula to remove branched calculi. A conventional resection of the UPJ is performed only in the case of an associated UPJ stenosis with a need for pyeloplasty. Calyceal stone fragments are removed with the use of an angulated calculi forceps; residual fragments can be dislodged with a pulsatile saline flow irrigation of the pelvicalyceal system.

To search for residual calculi and define their location, the physician can use either operative ultrasonography or renoscopy with a flexible endoscope or intraoperative radiographs using dental films as described by Braren.[187] At the end of the procedure, insertion of a nephrostomy tube or ureteral stent is a safe, although not routine, option, and a watertight pelvic closure is performed with fine absorbable suture. A Penrose or suction drain is left in the renal fossa to collect any extravasated urine, and the wound is closed.

Pyelotomy may be associated with segmental nephrotomies and is considered to be a safe and effective procedure with low morbidity. Much more invasive is anatrophic nephrolithotomy for the management of complete staghorn calculi with a large stone burden or multiple calyceal calculi.[6] The technique has been extensively described by Smith and Boyce.[188,189] The kidney is exposed and completely mobilized. The principle is to bivalve the kidney along an avascular plane between the anterior and posterior renal segment. The posterior branch of the renal artery is isolated and temporarily occluded with an atraumatic clamp. Injection of indigo carmine or methylene blue may serve to define the anatrophic line. The renal pedicle is clamped, and an ice slush is placed around the kidney within a rubber dam to ensure cold ischemia during the procedure. Careful monitoring of core body temperature is important to prevent systemic hypothermia and acidosis. The nephrotomy is performed along the anatrophic line, deep to the pelvicalyceal system. All the calculi are extracted with intraoperative renal radiographs. The pelvicalyceal system is then reconstructed using absorbable thin suture material. Optical magnification and microsurgical technique are necessary in infants and young children to reconstruct the collecting system without creating areas of stenosis along the infundibula. After careful progressive hemostasis of any bleeding point in the renal parenchyma, the renal capsule is tightly closed with a continuous locked suturing technique. Drainage of the renal cavities is not routine, but a Penrose-type drain should always be left in the renal fossa.

This procedure is associated with a high morbidity. Specifically, significant blood loss requiring transfusion is frequently encountered—in 6 of 11 patients reported by Assimos and associates[190] and in 3 of 9 patients more recently described by Gough and Baillie.[191] This heavy procedure does not guarantee a stone-free status; 2 of the 11 patients described by Assimos and associates and 1 of the 9 reported by Gough and Baillie had residual calculi. Also, the long-term consequences of this technique with prolonged hypothermic renal ischemia are still unclear because they have been studied in only a few children. Cendron and colleagues[192] reported on a series of five patients with preoperative and postoperative

Table 48-11 Results of Percutaneous Nephrolithotripsy in Children

Author	No. Patients	Patient Age	Procedure Nephroscope	Procedure Lithotripsy	Stone-free Rate (%)
Boormans et al[178]	23	16 mo–15 yr	16F	Ultrasonic/grasper forceps	58 (1 session)
					81 (at discharge)
Dawaba et al[179]	65	9 mo–16 yr	14F/30F	Ultrasonic/grasper forceps	86 (1 session)
					93 (at discharge)
Salah et al[180]	135	8 mo–14 yr	19F/26F	Pulsed dye laser	98.5
Desai et al[181]	56 complex calculi	6 mo–15 yr	20F/24F tract	Pneumatic/grasper forceps	56 (1 session)
			14F scope		90 (at discharge)
	72 noncomplex			EHL/holmium:YAG laser	97 (at discharge)
Sahin et al[182]	14	8-17 yr	24-30F tract	Ultrasonic/laser grasper forceps	69 (at discharge)
			14-28F scope		
Zeren et al[183]	55	10 mo–14 yr	18F-30F tract	Ultrasonic-pneumatic/grasper forceps	87 (at discharge)
					10% retreatment rate
Badawy et al[184]	60	3-13 yr	26F/28F tract	Ultrasonic/grasper forceps	83 (1 session)
			24F scope		90 (at discharge)
Rizvi et al[137]	62	4-14 yr	22F tract	Ultrasonic/grasper forceps	68 (1 session)
			19.5F scope		95 (after ESWL in 27%)
Jackman et al[169]	11	2-6 yr	11F	None	85 (at discharge)
			"Mini-perc"		45% retreatment rate
Mahmud and Zaidi[185]	29	1.4-5 yr	17F scope		60%
					100% when combined with ESWL

EHL, electrohydraulic lithotripsy; ESWL, extracorporeal shock wave lithotripsy.

renal scintiscans and observed no deterioration of renal function; however, more recently, Gough and Baillie[191] observed a significant decline (>5%) in differential function in five of nine children after surgery.

For these reasons, the indications for anatrophic nephrolithotomy in pediatric patients should be limited to the strict minimum. ESWL monotherapy or ESWL in association with minimally invasive procedures or pyelotomy, even if several treatment sessions are necessary, is probably a better option in most situations in which anatrophic nephrolithotomy is considered.

Ureteral Calculi

In view of the excellent results achieved with ESWL or ureteroscopy for the treatment of ureteral calculi in children, indications for an open procedure are exceptional, primarily when the calculus is associated with an obstructive uropathy such as a megaureter (however, it is not always easy to define whether the ureteral dilation is the cause or the consequence of the calculus). The ureter is approached via a retroperitoneal abdominal anterior incision; the level of the incision depends on the location of the stone. A vessel loop is passed around the ureter, above and under the calculus level, to prevent inadvertent migration. The ureter is incised longitudinally, and the stone is extracted with the use of an atraumatic forceps. A ureteral stent is not routinely inserted, and the ureteral incision is closed with the use of fine absorbable suture material. A retroperitoneal Penrose-type drain is inserted, and the wound is closed.

Laparoscopy

Most procedures performed by open surgical techniques can now be performed using a transperitoneal or retroperitoneal laparoscopic approach, including total or partial

Table 48-12 Complications of Percutaneous Nephrolithotripsy in Children

Author	No. Patients	Blood Transfusion	Urinary Leakage	Sepsis	Other	Total (%)
Boormans et al[178]	23	1	—	1	—	8.6
Dawaba et al[179]	65	1	—	—	Pelvic perforation: 1	3
Salah et al[180]	135	10 (7%)	11 (8%)	—	Urinoma: 10 (7%)	22
Desai et al[181]	56 complex	14%	5.4%	5%	—	24.4
	72 simple	5.4%	—	5.5%	—	10.9
Zeren et al[183]	55	24%	5%	—	Broken wire in distal ureter: 1	29.5
Badawi et al[184]	60	2	1	—	Colonic perforation: 1	6.6
Rizvi et al[137]	62	17 (25%)	4 (6.4%)	—	Hydrothorax: 1	35.5
Mahmud and Zaidi[185]	29	2 (7%)	—	—	Retention: 1	10

nephrectomies, pyelotomies, and ureterotomies (Fig. 48-16). These techniques have been reported in a few patients.[193] There is little doubt that in the future the laparoscopic approach will overcome conventional surgery in these indications and where, owing to stone recurrence, consecutive procedures would have been necessary in the past, leading to multiple scars in patients.

Lower Urinary Tract Calculi

Bladder Calculi

In developed countries, bladder calculi are rare and are mainly encountered in patients with anatomic or functional abnormalities of the bladder (Fig. 48-17). Bladder stone is one of the most frequent long-term complications after bladder neck plasty to treat incontinence in patients with exstrophy epispadias[194]; postvoiding residue and infection are the most probable lithogenic factors in these patients. Bladder calculi are also a classic complication after augmentation with intestinal patches (incidence 10% to 50%).[195] Stones are almost exclusively made of struvite and calcium phosphate and related to chronic bacteriuria, incomplete bladder emptying, and mucus production; staples are also a predisposing factor.

Kronner and associates[195] reviewed the records of 286 patients who underwent bladder augmentation; the incidence of stone formation was 10% and was similar with ileum and colonic patches. They observed that the incidence of stone formation was only 6% after enterocystoplasty alone, 14% after enterocystoplasty associated with either a bladder neck procedure or a catheterizable stoma, and 21% when enterocystoplasty was associated with procedures increasing bladder outlet resistance and catheterizable stomas. Frequent and complete emptying of the reservoir and regular evacuation of mucus are important factors to prevent stone formation in this population. Use of a gastric patch for augmentation seems to decrease the risk of bladder stone significantly. Gastrocystoplasties are associated with other serious complications, however, such as the hematuria-dysuria syndrome; ureterocystoplasties, detrusorotomies, and augmentations using intestinal segments that have had demucosation performed are probably better alternatives.

In developing countries, the incidence of bladder calculi is much higher, representing a major health problem (Fig. 48-18). In 1986, Srivastava and coworkers[196] reported on 132 children with bladder stones seen in 1 year at a single institution in Afghanistan; 94% were boys, and 73% were 1 to 5 years old. This endemic disorder is thought to be related to dietary factors, mainly to consumption of a predominantly cereal-based diet. In these populations, milk, dairy products, eggs, and meat are not eaten on a daily basis. Endemic bladder stones are composed of calcium oxalate and uric acid, and recurrence is uncommon after their removal. Repeated attacks of diarrhea and dehydration lead to the passage of a concentrated, acidic urine, and a high oxalate load may be provided by a high consumption of tea, nuts, and green leafy vegetables. Srivastava and coworkers[196] mentioned that the disease declines in areas where milk and eggs become more available.

The principles of management of bladder stones are similar to those for upper urinary tract calculi. The calculus is approached by the least invasive technique, either removed in one piece or fragmented and then all the fragments removed to avoid recurrences, and the treatment must not create lesions to the lower urinary tract or adjacent structures. The calculus can be approached via an endoscopic route, a suprapubic percutaneous access, or a conventional open cystotomy. The endoscopic approach is appropriate in most patients with a patent urethra and bladder neck and a limited stone burden, particularly in boys, where prolonged transurethral procedures carry the risk of subsequent urethral stricture development. Any means of stone fragmentation previously described (electrohydraulic, ultrasonic, ballistic, or pulsed laser) may be used according to the operator's experience and equipment.[197,198] Great care should be taken not to perforate the bladder during fragmentation, mainly with electrohydraulic shocks, and not to traumatize the urethral mucosa during the removal of fragments.

When the endoscopic route is inaccessible, particularly in patients who have had a bladder neck closure, or when there is a large stone burden, a suprapubic percutaneous access can be created. The bladder is filled with saline, then punctured; the tract is dilated sufficiently to permit the introduction of an Amplatz sheath through which endoscopic instruments can be inserted to allow lithotripsy and removal of fragments. The tract can eventually be overdilated to 34F, as described by Elder,[199] to allow introduction of a large endotracheal tube to remove large calculi without the need of lithotripsy. Van Savage and associates[200] introduce a suction tube suprapubically, and the stones or fragments remaining after EHL are aspirated under direct visualization via cystoscopy through the urethra or via a second suprapubic puncture.

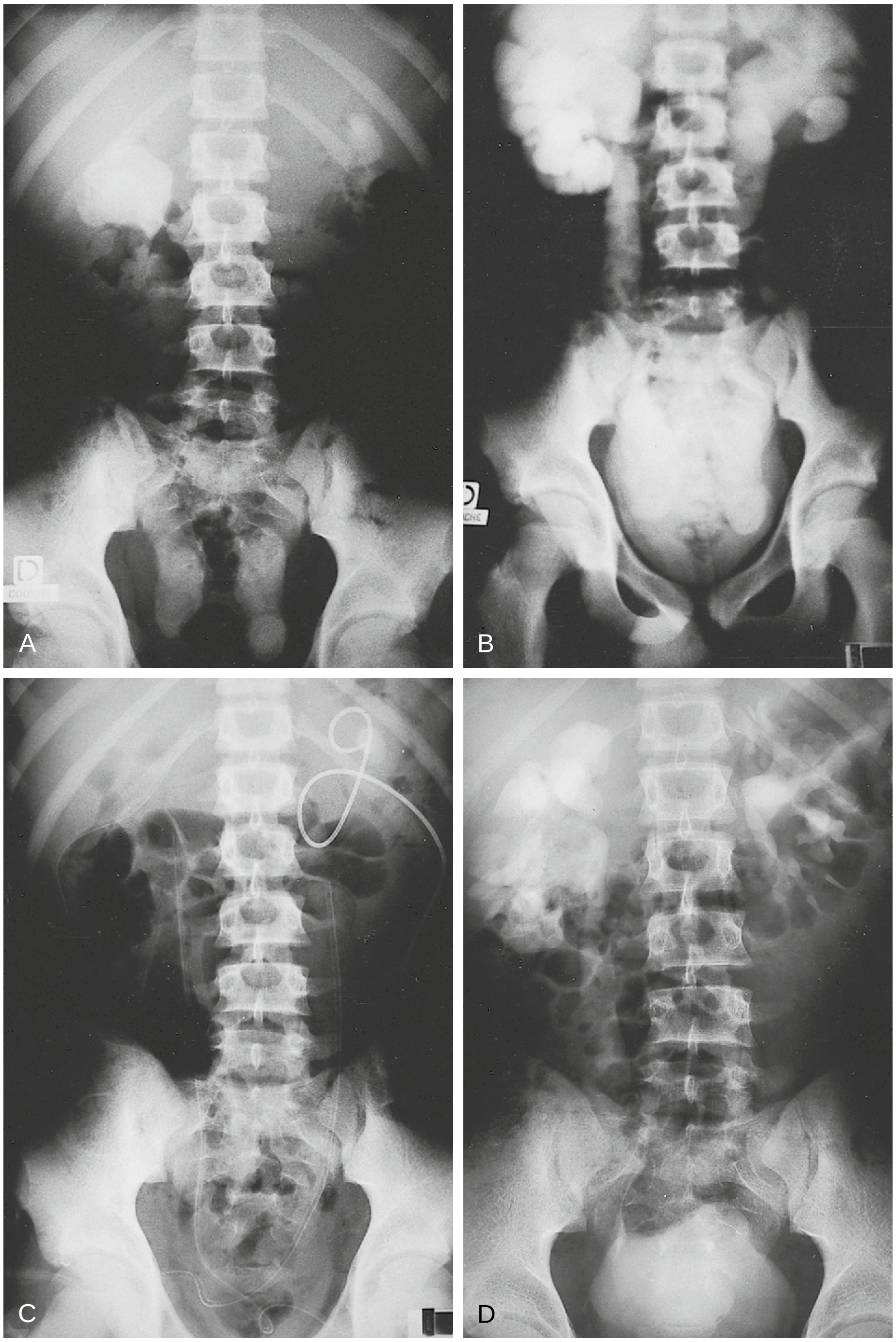

Figure 48-15 **A,** KUB (kidney, ureter, and bladder) film shows bilateral renal and ureteral stones in a 13-year-old boy. **B,** Preoperative IVP. **C,** Result after right pyelotomy and a bilateral ureteral reimplant after stone extraction in a single session. **D,** Postoperative IVP after a single extracorporeal shock wave lithotripsy session treatment on the left kidney.

The use of percutaneous suprapubic cystolithotripsy for vesical calculi in children has been reported to be effective with minimal morbidity and short hospital stay by numerous authors,[201-203] and it seems particularly appropriate for the treatment of endemic lithiasis. This approach can also be used for calculi in augmented bladders; however, it carries the risk of intraperitoneal extravasation of irrigating fluid. To prevent this complication, Elder[199] recommended that the site of the old reservoir drainage tube be used for percutaneous access because at this point the augmented segment is fixed to the anterior abdominal wall. When treating patients endoscopically via either transurethral or percutaneous access, it may prove challenging to remove all the fragments from a large, irregular reservoir. Although there was no statistically significant difference between the two treatment groups, Kronner and coworkers[195] observed that 6 (54%) of 11 patients treated endoscopically had recurrent stones compared with 5 (33%) of 15 treated with open surgery. Although it is more invasive than endoscopic techniques, open cystolithotomy is still an alternative to augmented reservoirs or in departments in developing countries that are not fully equipped. The procedure is generally simple and fast and requires a short hospital stay with a minimal morbidity.

Urethral Calculi

Urethral calculi are almost exclusively a male pathology. Either they come from the bladder and are stopped in their migration because they are too large for the caliber of a normal urethra, or they are a result of urinary stasis above a urethral stricture or within a urethrocele. In both cases, they are usually revealed by infection, pain during micturition, or acute urinary retention.

The treatment strategy depends on whether the stone is associated with a urethral abnormality. When the urethra is normal, the main concern is to avoid urethral trauma with the risk of subsequent stricture. Usually the best option is to dislodge the calculus and push it back to the bladder, where it is fragmented. The fragments can be extracted without trauma to the delicate urethral mucosa. When the stone is associated with a urethral stricture or urethrocele, both treatment

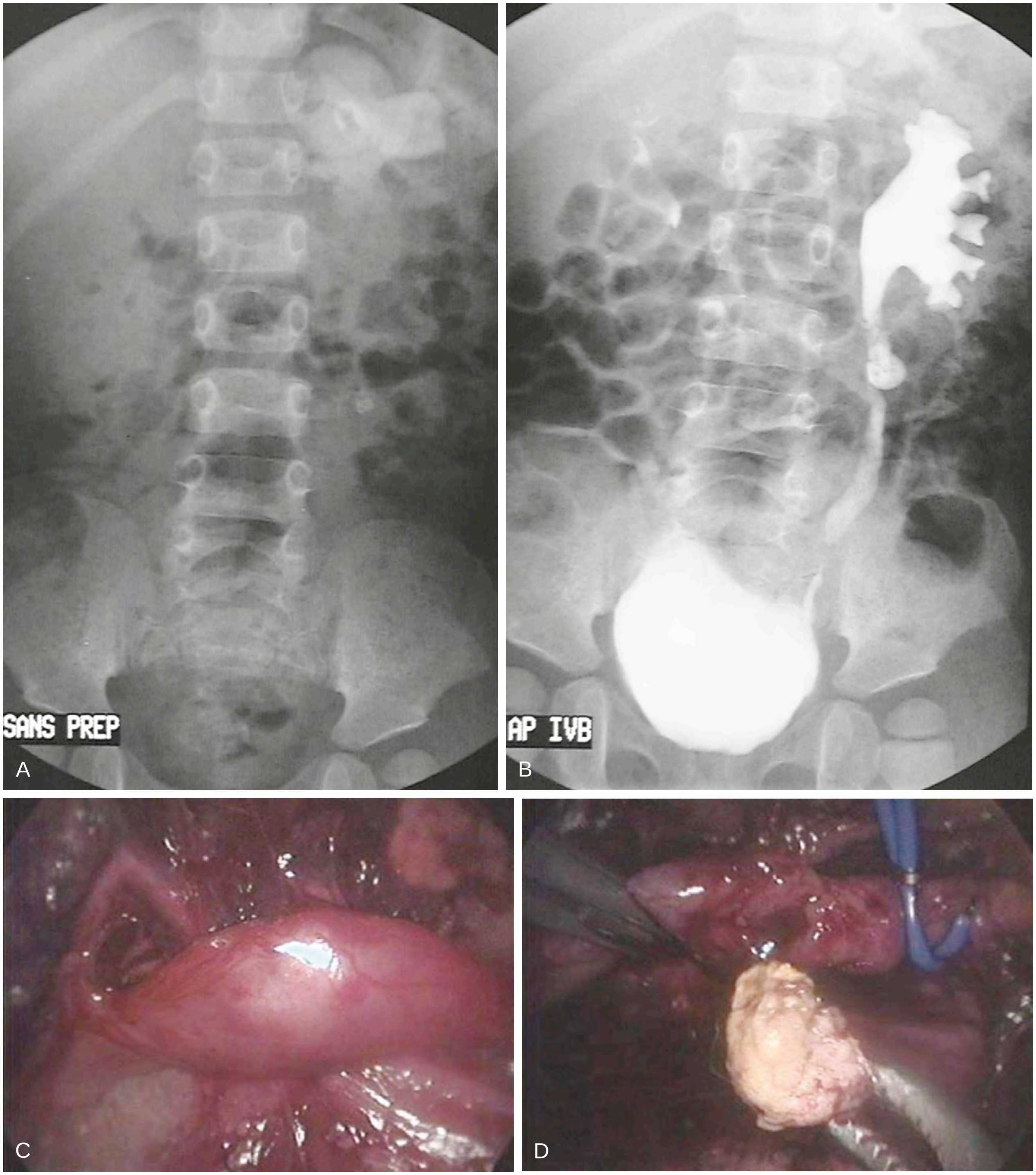

Figure 48-16 **A,** A 6-mm upper ureteral stone in a 2-year-old girl. **B,** On IVP, the stone is stopped in its migration at the level of a partially obstructive ureteral loop. **C,** Under general anesthesia, the patient was placed in a left lumbotomy position, and using three 5-mm ports, the calculus and a vascular loop were identified. **D,** The calculus was extracted through a longitudinal ureterotomy.

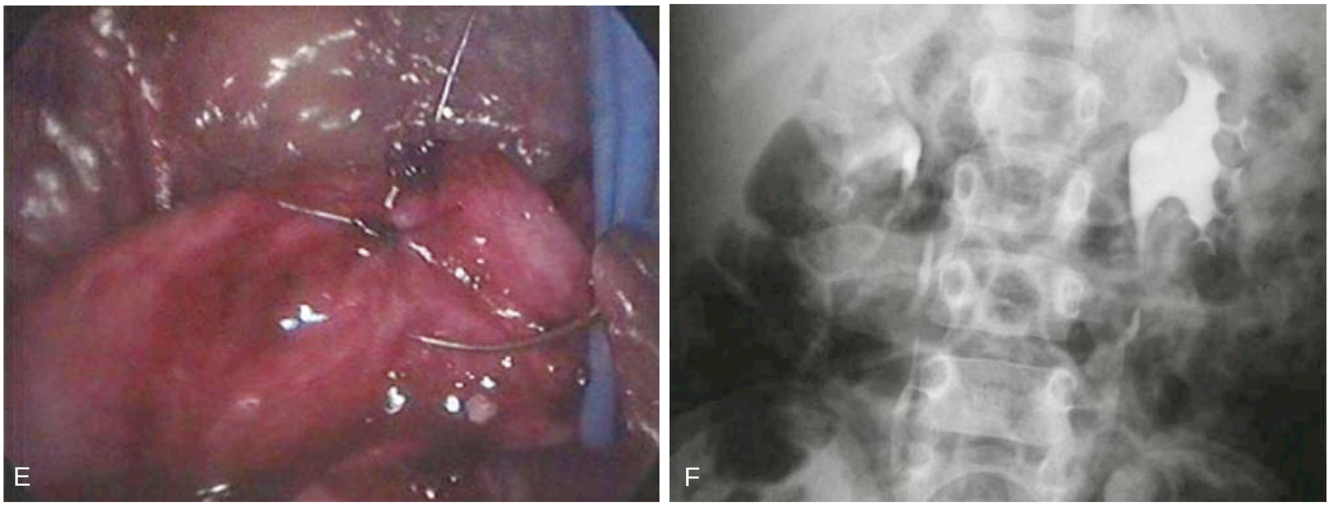

Figure 48-16, cont'd **E,** The ureterotomy was closed with endocorporeal separate stitches, and the vascular loop was transected. **F,** Normal postoperative IVP at 3 months.

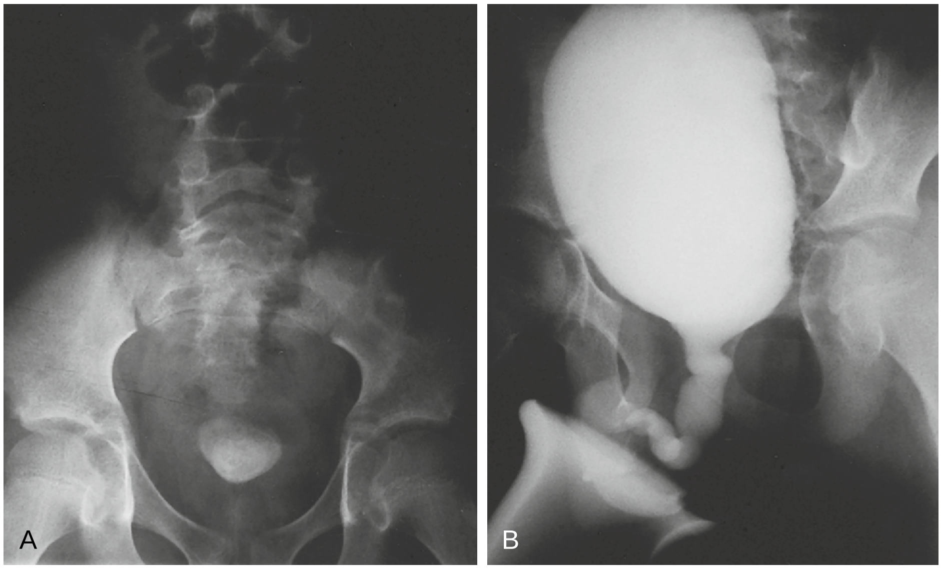

Figure 48-17 **A,** Bladder stone after failed hypospadias repair. **B,** Voiding cystourethrography in the same patient.

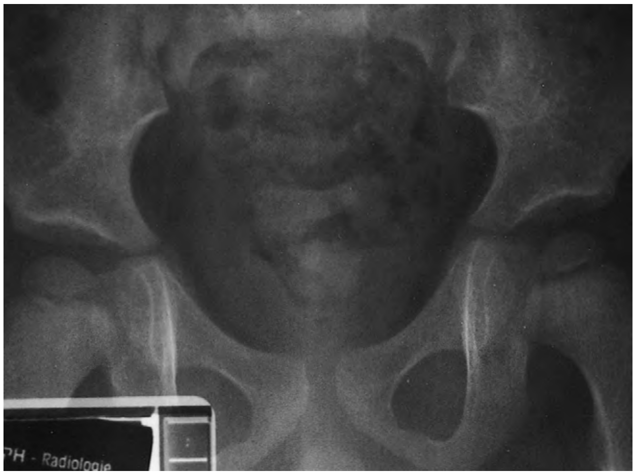

Figure 48-18 Endemic bladder lithiasis in a 3-year-old boy.

of the urethral abnormality and extraction of the stone are performed in one or two steps, usually by open surgery.

REFERENCES

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PART VIII

UROGENITAL TUMORS

CHAPTER 49

ONCOLOGIC PRINCIPLES OF PEDIATRIC GENITOURINARY TUMORS

Fernando A. Ferrer

Collectively, Wilms' tumor, non-Wilms' renal tumors, and rhabdomyosarcoma represent a significant proportion of solid tumors in children. Pediatric urologists can assume that they will be involved in the care of these patients as a primary or consulting provider. In contrast to adult cancers, in which environmental exposures are a significant causal factor, pediatric cancers are often associated with identifiable genetic events. The clinician must be familiar with these events to understand prognostic molecular features of pediatric tumors, counsel families, and interact with colleagues.

Surveillance, Epidemiology, and End Results (SEER) data show that significant progress has been made in the treatment of pediatric cancer over the last 30 to 35 years. Early on, SEER data for children 5 to 9 years old with all cancers showed 5-year survival to be 55.4%; this increased to 78.3% in years 1995-2000.[1] Much of this progress has been the result of work done by large collaborative groups, such as the Children's Oncology Group (COG), which facilitate a multidisciplinary approach to treatment. Today, roughly 90% of children treated in the United States receive their care at COG member institutions.[2]

WILMS' TUMOR

Initially described in seven children by Wilms in 1899, Wilms' tumor is an example of success in treatment and understanding of childhood cancer.[3] Initial success through surgical treatment was followed by multimodality therapy, leading to an approximately 90% overall survival. Recent decades have seen a dramatic increase in understanding of the genetic and molecular features of this cancer. Today, the focus of therapy is on tailoring treatment without compromising survival and expanding knowledge of the molecular biology of this cancer.

Molecular Biology

WT1

The clinical observation that patients with aniridia, genital anomalies, and mental retardation developed Wilms' tumor at a higher rate than the general population led to the discovery of a heterozygous deletion at 11p13 by cytogenetic analysis.[3-6] Cloning techniques subsequently identified the *WT1* gene. The association with aniridia occurs because the *PAX6* gene, which is important to eye development, resides adjacent to *WT1* and is affected by the deletion abnormality.[7]

The *WT1* gene encodes a 55-kD zinc finger transcription factor that is commonly believed to function as a tumor suppressor. Support for this theory comes from factors including similarities in structure between it and other known transcription factors, such as an amino terminus rich in prolines and glutamines.

Alternative splicing results in multiple different isoforms of *WT1*. The two isoforms most commonly recognized at this time are alternative splice I (variable insertion at exon 5), which is unique to mammalian cells, but whose role in vivo is not clearly understood, and alternative splice II (also known as KTS).[8] Alternative splice II (+KTS) alters the DNA binding properties of *WT1*, affecting the development of the gonads and kidneys in Frasier syndrome.[8] Other variations may result from alternative translation initiation sites.

WT1 mutations are present in a minority of patients with Wilms' tumor and do not have a major impact on prognosis. These patients frequently exhibit stromal predominant pathology. Several downstream targets of *WT1* have been identified, including EGFR, PDGF, IGF, N-*myc*, *MDR-21*, and *P-21*, all of which are associated with tumor development and are presumed to be the causal agents in Wilms' tumorigenesis.[9]

WT2

The identification of a second Wilms' tumor locus at 11p15 occurred as a consequence of the association of Wilms' tumor and Beckwith-Wiedemann syndrome. The connection between the two was initially identified by familial-linkage studies and cytogenetic analyses.[10] These studies pointed to inheritance of two copies of paternal chromosome 11 or duplication of the paternally derived 11p15 locus, resulting in germline mutations.

The specific gene responsible at 11p15 has not been identified, but several candidate genes have been suggested. One of the most attractive candidates is *IGF2* at 11p15. *IGF2* is a paternally expressed embryonic growth factor.[11,12] Studies in mice have shown that overexpression in transgenic mice leads to overgrowth, consistent with Beckwith-Wiedemann syndrome in humans.[13] Other genes implicated in Beckwith-Wiedemann syndrome include *H19* (fetal liver mRNA), *p57* (a cyclin-dependent kinase inhibitor), and *L1T1* (an untranslated RNA region adjacent to p57).[14]

Chromosomes 1p and 16q

In 1994, investigators from the Pediatric Oncology Group reported that some children in the third National Wilms' Tumor Study (NWTS-3) and NWTS-4 showing loss of heterozygosity

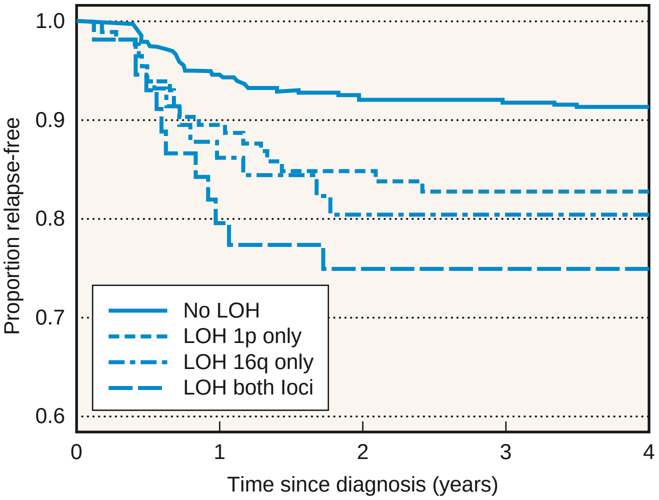

Figure 49-1 Relapse-free survival by joint loss of heterozygosity (LOH) at chromosomes 1p and 16q for stage VII favorable-histology Wilms' tumor patients. (From Grundy PE, Breslow NE, Li S, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol.* 2005;23:7312-7321.)

(LOH) for DNA markers on chromosome 1p or 16q or both seemed to have worse 2-year relapse-free survival than matched controls. NWTS-5 was designed to evaluate the prognostic significance of LOH at these sites in children with favorable-histology tumors. NWTS-5 determined the incidence of LOH at 1p and 16q to be 11.3% and 17.4%. LOH at 16q was significantly more common in patients with anaplastic Wilms' tumors than in patients with favorable histology. A similar, but nonsignificant trend was observed for abnormalities at 1p. LOH at these sites was also less common in younger patients.[15]

When considering all stages, there was a significant increased risk of relapse for patients with LOH at 1p and 16q (relative risk 1.56 and 1.49).[15] It was also shown that significant overlap existed between LOH at these sites. Patients harboring LOH at both sites had an even higher risk of relapse (Fig. 49-1).[15]

LOH did not correlate with site of relapse, and it was not a significant prognostic factor for clear cell sarcoma or rhabdoid tumor of the kidney.[15] LOH at 1p and 16q has been introduced in more recent COG protocols as a stratifying molecular marker, identifying patients at higher risk who would receive intensified therapy.

β-*Catenins*

β-Catenins are multifunctional proteins, related to the E-cadherin family, that are involved in the Wnt signal transduction pathway. Although not commonly known, activating mutations of β-catenins are among the most common somatic genetic lesions identified in Wilms' tumor.[16] These mutations frequently coincide with *WT1* mutations.[17] In the absence of degradation, β-catenins cross into the nucleus, where they interact with T cell–specific transcription factor and lymphoid enhancer factor, forming a transcription complex.[18] This complex activates factors that promote cell proliferation, survival, cellular invasion, angiogenesis, and immune invasion. A partial list of these downstream effectors includes c-*myc*, cyclin D, VEGF, IL-8, PPARd, and COX-2. Initial studies suggest that 10% or more of Wilms' tumors may harbor abnormalities of β-catenins.

TP53

More recent studies using microdissection techniques have identified that *TP53* mutations are commonly present in anaplastic areas of Wilms' tumors. Alternatively, in tumors with adjacent favorable-histology areas, *TP53* mutations are rare. These findings suggest that *TP53* mutations may be required for the development of anaplasia.[19] The role of p53 in tumorigenesis is well established; p53 induces cell cycle arrest and apoptosis in cells with DNA damage. Because of these findings, current COG protocols are evaluating the prognostic value of *TP53* mutations in patients with anaplasia.

WTX

Investigators have identified a new putative Wilms' tumor gene called *WTX*. Inactivation of *WTX* was identified in 15 of 51 tumors.[20] Tumors with *WTX* mutations lacked *WT1* mutations. The gene resides on the X chromosome. In contrast to the biallelic inactivation of an autosomal tumor-suppressor gene (Knudson's two-hit hypothesis), the *WTX* suppressor gene can be inactivated by a monoallelic "single hit" that targets the X chromosome in males and the active X chromosome in females.[20] This study has raised the question regarding the role of X chromosome genes in tumorigenesis.

Genetic alterations associated with Wilms' tumor have and continue to be carefully explored. A small percentage (approximately 10%) of Wilms' tumors arise as a result of germline mutations. Germline mutations occur in the germ cells of the patient and can be transferred to the patient's progeny. This group of patients represents the population studied by Knudson, which resulted in the application of the two-hit theory in Wilms' tumor patients.[4] The two-hit model requires that two genetic insults must occur for a tumor to develop. The first may occur as a result of inheritance of a germline mutation or a de novo germ cell aberration. These patients are predisposed to tumor development, requiring only one other event, or "hit," for a tumor to develop. The most commonly described scenario that fits the Knudson model is the inactivation of both alleles of a tumor-suppressor gene. The best example of this is the development of retinoblastoma in patients with inactivation of *RB1.*

Syndromes

Wilms' tumor patients with germ cell mutations are characterized by syndromic conditions, associated genitourinary anomalies, familial tumors, and tumors that develop at an earlier age than in patients with sporadic disease (Table 49-1). The association of *W*ilms' tumor with *a*niridia, *g*enitourinary anomalies, and mental *r*etardation has been recognized as the WAGR syndrome. Characterized by germline *WT1* mutations, WAGR syndrome also illustrates the importance of *WT1* for normal genitourinary development. Patients with WAGR syndrome typically have defects such as renal hypoplasia or ureteral, urethral, or gonadal abnormalities.

In contrast to WAGR syndrome, Denys-Drash syndrome, which is also associated with *WT1* abnormalities, is much more severe. An arginine-to-tryptophan change in exon 2 is the most common finding in patients with Denys-Drash syndrome.[21] This abnormality may lead to a dominant negative effect, whereby the mutated protein affects the function of the remaining wild-type protein by dimerization.[21]

Simpson-Golabi-Behmel syndrome is a rare congenital overgrowth syndrome; features include macroglossia, macrosomia, renal and skeletal anomalies, and an increased risk of cancer. The syndrome is related to the loss of function of the glypican-3 gene (*GPC3*) at chromosome Xq26.[22] The syndrome is complex and significantly overlaps with other overgrowth syndromes.[23]

Table 49-1 **Syndromes Associated with Wilms' Tumor and Estimated Risk**

Syndrome	Gene	Presenting Features	Tumor Risk
WAGR	11p13 (*WT1*)	Aniridia, genitourinary anomalies, retardation	30%
Denys-Drash	11p13 (*WT1*)	Genitourinary anomalies, renal failure, disorders of sexual development	90%
Frasier	11p13 (*WT1*)	Genitourinary anomalies, focal glomerular sclerosis, disorders of sexual development	Rare
Beckwith-Wiedemann	11p15	Organomegaly, macroglossia, hemihypertrophy	5%
Simpson-Golabi-Behmel	Xq26	Organomegaly, renal dysplasia, polydactyly, heart defects	7.5%

Wilms' tumor occurs infrequently in patients with Frasier syndrome. A specific mutation that affects the splice donor site at exon 9 seems to be involved[24]; this correlates with the important KTS insertion site of exon 9. The insertion of three amino acids at this point (lysine K, threonine T, serine S) results in the formation of different isoforms of *WT-1* (WT1$^-$KTS or WT1$^+$KTS). In Frasier syndrome, the relative ratio of +KTS to −KTS is altered.

The relationship of Beckwith-Wiedemann syndrome to 11p15 abnormalities was discovered on the basis of familial linkage syndromes. These studies showed either paternal duplication (paternal trisomy) or inheritance of two paternal chromosomes (unipaternal isodisomy).[25,26] Of the potential genes dysregulated in this syndrome, the *IGF2* gene is the most attractive candidate because it could also be responsible for the overgrowth phenotype.[11,12]

Familial Wilms' tumor is rare and constitutes only a small percentage of patients with constitutional *WT-1* anomalies. Two familial syndromes have been identified. The first, FWT1, is associated with abnormalities at 17q12-21 and carries a 20% risk of developing Wilms' tumor.[27] The second, FWT2, harbors 19q13.4 abnormalities, and patients have a 70% risk of Wilms' tumor.[28]

Prognostic Factors

Therapy for Wilms' tumor is determined by stratifying the individual patient's risk. Several clinical, pathologic, and biologic factors have been identified to be prognostic in Wilms' tumor and are used to stratify patients. We briefly review the principal risk factors before discussing principles of therapy. Chapter 50 provides details of surgical therapy and adjuvant treatment.

Tumor Stage

Stage is determined solely by the anatomic extent of the tumor. Tumors that are locally advanced or metastatic carry a worse prognosis than tumors that remain localized. The NWTS (now known as the COG Renal Tumors Committee) and the International Society of Pediatric Oncology (SIOP) staging systems have been shown to correlate well with outcomes. The principal difference is that the NWTS/COG system is a prechemotherapy, surgical based system, whereas the SIOP system stages patients after they have received chemotherapy. This fundamental difference precludes stage-by-stage comparisons of patients enrolled in the two groups.[29]

Histology

Histology remains the strongest predictor of outcome. In particular, anaplasia, defined by cells showing irregular mitosis, enlarged nuclei, and hyperchromasia, portends a poorer outcome compared with favorable-histology (standard triphasic) tumors.[30] Anaplasia is subdivided further into diffuse or focal categories. Focal anaplasia or anaplasia confined to one or a few discrete loci within a tumor carries a better prognosis than diffuse anaplasia.[31] NWTS/COG grading focuses on the presence of anaplasia, whereas the SIOP system grades tumors after chemotherapy. In the SIOP system, changes occurring in response to chemotherapy figure heavily. Three basic SIOP classifications exist: low risk, characterized by necrotic tumor or differentiated tumor; intermediate risk, characterized by regressive tumor, epithelial or stromal components or both, or focal anaplasia; and high risk, characterized by blastemal or diffuse anaplasia.[29,32]

Patient Age

Age younger than 2 years with small favorable-histology tumors (<550 g) has been associated with an excellent prognosis.[33,34] This observation led to the incorporation of a surgical treatment–only arm in NWTS-5 for patients with stage I tumors that met the above-mentioned criteria. After treating 75 patients, the study was closed because at 2 years 13.5% of patients had relapsed. All of these patients were salvaged with standard chemotherapy.[34] Current plans call for revisiting this strategy in future COG protocols.

Biologic Factors

As discussed previously, patients with LOH at chromosomes 1p and 16q have higher recurrence and mortality rates. LOH at these sites may explain the poor outcomes of 5% of favorable-histology patients. COG studies are expected to stratify these patients to receive more aggressive therapy. The presence or absence of *WT-1* mutations does not significantly alter outcome. Patients with p53 abnormalities seem to do poorly relative to patients without p53 abnormalities. p53 abnormalities are commonly associated with anaplasia.[35,36]

Treatment Overview

Current treatment for children with Wilms' tumor focuses on limiting therapy for patients in low-risk groups and intensifying treatment for patients at risk for failure or relapse.

Low-Risk and Standard-Risk Patients

The very-low-risk, low-risk, and standard-risk protocol from COG studies eliminates chemotherapy for select patients with favorable-histology, low-volume disease, and uses biomarkers to predict low-risk patients at risk for relapse. In NWTS-5, children younger than 2 years with tumors weighing less than 550 g were initially treated with nephrectomy alone. Of 75 children treated in this fashion, 11 relapsed. Five patients had pulmonary relapse, three had flank disease, and three had contralateral disease. The study was stopped because initial stoppage criteria were met; however, the salvage rate for relapsing patients treated with chemotherapy and radiation was 91%. Based on these findings, the current protocol calls for nephrectomy only in young patients with low-volume disease.

Future studies are expected to provide insight into the role of chemotherapy in preventing metachronous contralateral tumors arising from nephrogenic rests. Patients with low-stage (I and II), favorable-histology disease would receive two agents: vincristine and dactinomycin. Similar patients with LOH at 1p and 16q would have doxorubicin added and be classified as standard as opposed to low risk.

In NWTS-5, stage III patients with favorable histology experienced an 83% relapse-free survival and an overall survival of 93.9% using three-drug therapy and radiation. This group of patients would continue to receive three-drug therapy and radiation, and would be classified as "standard risk." Further evaluation of this population showed that patients with LOH at 1p and 16q had a 65.9% event-free survival and a 75% overall survival. As a consequence, stage III patients with LOH would be enrolled in the favorable-histology high-risk protocol.

Favorable-Histology, High-Risk Patients

There are two primary objectives in the favorable-histology, high-risk protocol. The first is to attempt to spare a subgroup of patients with pulmonary metastasis radiation therapy. This protocol would exempt patients who respond to three-drug therapy with disappearance (as shown by computed tomography scan) of all pulmonary metastasis by week 6 of treatment from pulmonary radiation. This protocol is modeled after a similar successful approach adopted by European investigators. Patients with metastasis remaining at 6 weeks would go onto radiation therapy. The second objective is to attempt to improve outcomes of stage III and IV favorable-histology patients who have LOH at 1p and 16q by the intensification of chemotherapy.

High-Risk Patients

The presence of cellular anaplasia is the strongest predictor of outcome for patients with Wilms' tumor. Patients with focal or diffuse anaplasia are enrolled in a separate high-risk protocol. Patients with high-risk non-Wilms' tumors, such as clear cell sarcoma, malignant rhabdoid tumor, and pediatric renal cell carcinoma, are also addressed in this protocol. Relative to Wilms' tumor, primary study goals include the impact of cyclophosphamide/carboplatin/etoposide alternating with vincristine/doxorubicin/cyclophosphamide in patients with diffuse anaplasia, and the role of vincristine in combination with irinotecan for patients with metastatic anaplastic Wilms' tumor. This study also is expected to evaluate secondary questions, such as the outcomes of patients with focal anaplasia treated with three-drug therapy and radiation, and molecular questions regarding *TP53* mutations.

Late Effects

The long-term deleterious effects of childhood cancer therapy are increasingly being recognized. An example of this is a report from the Childhood Cancer Survivors Study, which evaluated more than 10,000 survivors of childhood cancer. Among this group, 62.3% had one chronic health condition, and 27.5% had experienced a severe or life-threatening condition after treatment.[37] For these patients, the adjusted relative risk of these events was significantly higher than for their normal siblings. The authors concluded that "survivors of childhood cancer have a high rate of illness owing to chronic health conditions."[37] Long-term complications associated with treatment of Wilms' tumor have been the focus of institutional and collaborative group reports. COG is actively studying this population via the National Wilms' Late Effects Study.

Secondary Cancer

A review of more than 5000 NWTS patients that were enrolled between 1969-1991 identified 43 secondary cancers compared with an expected number of 5.[38,39] This evaluation suggests a bona fide increased risk in patients treated for Wilms' tumor. Further analysis showed a significant positive correlation between dose of radiation and risk of secondary cancer. The addition of doxorubicin to radiation also seemed to increase risk. Hematologic and solid tumors were identified.[40] A significant concern was that the latency interval for solid tumor occurrence was 16 years, without plateau, suggesting indefinite follow-up to be appropriate.

Cardiovascular Disease

Treatment with doxorubicin is a known risk factor for cardiovascular disease. Initial evaluation of risk in Wilms' tumor patients estimated that the cumulative risk at 20 years was 4.4%.[41] Factors associated with increased risk included female gender; total dose of doxorubicin; and radiation to left side of heart, abdomen, or lung. More recently, the long-term cumulative risk has been recalculated to be 1.2%, with patients having left-sided tumors at a considerably higher risk.[42]

Pulmonary Complications

Pulmonary complications have been primarily associated with radiation exposure to the lungs. Of approximately 6500 patients treated in NWTS-1–NWTS-4, 67 developed pulmonary fibrosis.[43] In this study, patients were placed into four groups for analysis. Group 1 consisted of patients who did not receive radiation. Group 2 patients received radiation that did not include the lungs. Group 3 patients received pulmonary radiation. Group 4 comprised group 1 and 2 patients who went on to receive pulmonary radiation therapy. The incidence of pulmonary complications 15 years after treatment was 0.1% for group 1, 0.3% for group 2, 4.4% for group 3, and 5.3% for group 4.[43] Cyclophosphamide treatment seemed to increase risk among patients receiving radiation therapy.[43]

Renal Failure

The risk of renal failure in patients treated for Wilms' tumor has been studied extensively. Total incidence was reported to be 17% among patients with bilateral disease and 1% among patients with unilateral disease.[44] A subsequent analysis excluded patients developing renal failure as a result of bilateral nephrectomy. This analysis determined the rates of failure for patients with Denys-Drash syndrome, patients with WAGR syndrome, and male patients with genitourinary anomalies to be 62.4%, 38.3%, and 10.9%.[45] Patients with bilateral and unilateral disease had rates of 5.5% and 1%. Patients with WAGR syndrome developed renal failure after puberty; patients with Denys-Drash syndrome typically developed renal failure after puberty. As anticipated, patients with *WT1* anomalies had higher rates of end-stage renal disease.[45]

Growth

Children treated with flank radiation are at particular risk for somatic growth problems because the radiation fields encompass the spine. Evaluation of patients treated during NWTS-1–NWTS4 showed the growth deficit in children treated with 10 Gy of radiation therapy before age 1 year to be 7.7 cm. For children treated at age 4 with 10 Gy, the deficit was reduced to 1.1 cm. Younger patients are at greater risk.[46]

Fertility

Evaluation of male patients receiving radiation showed that their offspring had no significantly greater incidence of prematurity or low birth weight. Conversely, radiation had clear adverse effects on the offspring of mothers treated for Wilms' tumor. Duration of pregnancy and birth weights of newborns were significantly negatively affected by a history of radiation exposure.[47,48] Congenital malformations also were more common in children of irradiated mothers: 12% versus 3.2% (P = .03). Available data also suggest that female patients undergoing abdominal/pelvic radiation have a poor outlook for fertility.[47,48]

CLEAR CELL SARCOMA AND MALIGNANT RHABDOID TUMOR

Clear cell sarcoma is the second most common malignant renal tumor in young children. Currently, no molecular markers have been identified, and the pathogenesis of the lesion is poorly understood. A report from the COG Renal Tumors Committee concluded that clear cell sarcomas arise from renal mesenchymal cells and express multiple neural markers. Pathways involved may include sonic hedgehog, PI3K, and AKT.[49]

Data from NWTS-5 have shown that patients treated with cyclophosphamide/etoposide alternating with vincristine/doxorubicin/cyclophosphamide had improved survival relative to prior NWTS trials. With modifications of the above-mentioned regimen, it is hoped that overall survival for all stages will exceed 75%.

Malignant rhabdoid tumor was originally described in 1978 as a variant of Wilms' tumor, and was subsequently reclassified as a distinct entity in 1981.[30,50] The lesion has been reported at multiple sites outside the kidney and has been associated with loss of the *hSNF/InI1* tumor-suppressor gene.[51] The gene localizes to the 22q11.2 chromosome region and encodes a 47-kD protein, SWI/SNF, which plays an important role in chromatin remodeling and transcription regulation.[52,53]

The prognosis for patients with rhabdoid tumors is typically poor. Patients with localized disease (stage I and II) have experienced less than 50% survival. Rates are even poorer for patients with advanced disease. These patients are treated under the current high-risk protocol of COG, as are patients with anaplasia.

PEDIATRIC RENAL CELL CARCINOMA

Approximately 500 malignant neoplasms of the kidney are diagnosed in children each year in the United States, and most of these are Wilms' tumors. Renal cell carcinoma accounts for only 5.4% of renal malignancies in patients younger than 20 years.[54] Renal cell carcinoma has been documented in a 3-month-old infant, but the mean age at diagnosis of renal cell carcinoma in children is 8 to 11 years.[55-59] In contrast to adult renal cell carcinoma, no clear male preponderance has been shown in children. Several series have suggested that girls outnumbered boys.[55-59] Racial differences in incidence have also been noted in children, with some studies reporting a higher incidence among African-Americans; however, the small number of patients in these reports limit the ability to draw any significant conclusions.[58] In addition, although adult renal cell carcinoma has been associated with multiple environmental factors, such as cigarette smoking, analgesic abuse, and dialysis, few environmental risk factors are associated with pediatric cancer in general, and none have been identified for pediatric renal cell carcinoma.[60]

Molecular Biology

In 1986, it was shown that pediatric papillary renal cell carcinoma is associated with a translocation, or fusion of genes, located on separate chromosomes. The translocation typically affects genes located on chromosomes X and 1.[61] In 1996, the specific loci on chromosome X and 1 involved in this translocation were identified.[62] The translocation results in a fusion of the papillary renal cell carcinoma (*PRCC*) gene in the 1q21.2 region with the transcription factor E3 (*TFE3*) gene in the Xp11.2 region. A PRCC-TFE3 fusion protein is produced, and normal transcription is disrupted, leading to the development of papillary renal cell carcinoma.[62]

The *TFE3* gene product is a member of the MiT family of basic helix-loop-helix transcription factors, which include TFEB, TFEC, and MiTF.[55,63] This family of transcription factors has been implicated in various tumors, including melanoma, alveolar soft part sarcoma, and renal cell carcinoma.[62,64-67] It is hypothesized that the upregulation of any of these genes leads to an unbalanced ratio of transcription factors that may change downstream signaling mechanisms, resulting in renal cell carcinoma, or other tumors.[68] Multiple fusion genes involving *TFE3* have been associated with papillary renal cell carcinoma, including translocations with the *PSF* (splicing factor) gene, *ASPL* (alveolar soft part sarcoma locus) gene, and *CLTC* (clathrin heavy-chain) gene.[69-74] These translocations are extremely rare in adult renal cell carcinoma (<1% of tumors harbor translocations). More typical in adults is either *VHL* in conventional renal cell carcinoma or a duplication of the *MET* gene on chromosome 7 in papillary renal cell carcinoma.[75]

Treatment

Chemotherapy, radiation, and immunotherapy all have been used in pediatric renal cell carcinoma; however, none have been studied in a prospective fashion. A review of various series indicates that prognosis is not affected by adjuvant treatment.[76-80] Although it has been suggested that the PRCC-TFE3 fusion may disrupt the mitotic checkpoint in the cell cycle, making these cells sensitive to conventional microtubule-targeted chemotherapy agents, this has not been shown in any trial so far.[81]

The relatively good survival for children with localized renal cell carcinoma (including patients with local lymph node involvement), combined with the relative inefficacy of the best treatments for renal cell carcinoma, support treating patients with localized disease without adjuvant therapy. Patients with advanced renal cell carcinoma are encouraged to seek treatment with immunotherapy or phase I/II studies.

Table 49-2 **Syndromes Associated with Rhabdomyosarcoma**

Syndrome	Characteristics	Gene
Li-Fraumeni	Sarcomas, breast tumors, brain tumors, adrenal tumors, leukemia	*TP53*
Neurofibromatosis	Neurofibromas, rhabdomyosarcoma, glioma, skeletal dysplasia	*NF1*
Basal cell nevus (Gorlin)	Overgrowth, skeletal abnormalities, benign tumors, rhabdomyosarcoma, malignant tumors	*PTC*

RHABDOMYOSARCOMA

Rhabdomyosarcoma was first described in 1850 by Wiener.[82] Subsequently in the 1950s, Horne and Enterline published a histologic classification system that remains the basis for the system that is used today.[83,84] Since the 1950s, the outcomes of children with bladder/prostate rhabdomyosarcoma have improved significantly. Progress has largely been due to collaborative trials, such as those conducted by the Intergroup Rhabdomyosarcoma Study (IRS).

Molecular Biology and Syndromes

The international classification system for rhabdomyosarcoma includes embryonal, alveolar, pleomorphic, and undifferentiated subtypes.[84,85] Embryonal sarcomas constituted 73% of bladder/prostate rhabdomyosarcomas registered in the IRS studies from 1998-2004. Previously, it was believed that this subtype made up greater than 90% of bladder/prostate tumors.[86,87] Embryonal rhabdomyosarcoma resembles fetal striated muscle correlating to a gestational age of 7 to 10 weeks. Tumors are composed of spindle-shaped cells with a central nucleus in an eosinophilic cytoplasm. Microscopically, cross-striation is seen in 30% of cases.[88] Pathologic diagnosis is made by the morphologic identification of the tumor and the presence of "spotty" nuclear staining for myogenin or MyoD1. In contrast, diffused nuclear staining of myogenin or MyoD1 is seen with alveolar rhabdomyosarcoma.[89] Sarcoma botryoides is a subtype of embryonal tumor that has a favorable prognosis. The spindle cell variant of embryonal rhabdomyosarcoma is most common in the paratesticular region, and typically carries an excellent prognosis.[85]

Alveolar rhabdomyosarcoma constitutes about 15% to 20% of all rhabdomyosarcomas; it is uncommon in the bladder or prostate. Alveolar rhabdomyosarcoma occurs most frequently in older children and histologically resembles 10- to 21-week gestational age striated muscle. Histologic features include clusters of small round cells that are adherent to fibrosepta, creating well-defined alveolar spaces; cross-striations are uncommon. The alveolar subtype is more common in the extremities and trunk. Understanding of the molecular basis of this lesion has been advanced by the recognition that it harbors distinct molecular alterations, such as t(2;13) or t(1;13) translocations.[90] The more common t(2;13) translocation results in a *PAX3-FKHR* gene fusion, and the t(1;13) translocation corresponds to a *PAX7-FKHR* gene fusion. Sorensen and colleagues[90] noted that in patients with metastatic disease, *PAX3-FKHR* fusion resulted in a significantly higher rate of relapse and death. Patients with *PAX3-FKHR* fusion also seemed to have a greater predisposition for bone marrow metastasis. These molecular derangements continue to be explored as biomarkers of disease.

Pleomorphic rhabdomyosarcoma is not commonly found in the bladder or prostate of children. It may occasionally manifest in the bladder of adults, however.[91,92] The undifferentiated subtype is often difficult to identify because of a lack of antigenic markers and nonspecific large, round cells, with scant cytoplasm. This tumor can be confused with Ewing sarcoma, and in difficult cases, identification of t(2;13), t(1:13) translocations specific for rhabdomyosarcoma or t(11:22) specific for Ewing sarcoma can be helpful.[93,94] Occasionally, these tumors can be differentiated by immunohistochemical identification of specific muscle proteins, such as actin, myosin, desmin, and myoD, or, alternatively, electron microscopy can be used to identify Z bands associated with actin-myosin bundles specific to rhabdomyosarcoma.[95-97]

Genetic analysis of embryonal and alveolar subtypes of rhabdomyosarcoma has identified numerous common abnormalities, including the previously described *PAX-FKHR* gene fusions, expression of regulatory factors such as MYOD1 and myogenin, retinoblastoma pathway mutations, and p53 pathway mutations.[98] Until more recently, which individual or combined alterations could cause cell transformation was unknown. Sharp and associates[99] have reported that mice with inactivated *INK4a/ARF* (cyclin-dependent kinase inhibitor/alternate reading frame), which overexpresses hepatocyte growth factor/scatter factor, almost uniformly develop rhabdomyosarcoma with high penetrance and short latency. Although the similarity of this model to human rhabdomyosarcoma is unclear, the authors describe a unique animal model for further study.[99] Deletions of *INK4a/ARF* have an effect on retinoblastoma and p53 pathways, which are suspected to be important in rhabdomyosarcoma.

Various syndromes have been associated with rhabdomyosarcoma. Table 49-2 summarizes three of the most common.

Table 49-3 **Outcome in Rhabdomyosarcoma**

Histology	Prognosis	5-Year Survival
Sarcoma botryoides, spindle cell	Favorable	90%
Embryonal, pleomorphic	Intermediate	65-75%
Alveolar, undifferentiated	Unfavorable	40-55%

Prognosis

In addition to stage of disease and treatment risk groups, histologic classification continues to be one of the strongest predictors of outcome in rhabdomyosarcoma (Table 49-3).

Prognostic Significance of Rhabdomyoblasts

Significant controversy has surrounded the identification of rhabdomyoblasts in post-treatment specimens.[100] The principal question faced by clinicians is whether this finding requires further treatment, such as surgery. Analysis of postcystectomy specimens has shown rhabdomyoblasts with a reduction in cellularity in patients treated with chemotherapy, suggesting that this pattern may be indicative of response to therapy. Initial case reports suggested that observation was appropriate for these patients. Chertin and coworkers[101] reported the long-term follow-up of a patient with residual atypical cells after treatment with bladder rhabdomyosarcoma that had not recurred after 5 years.

Ortega and associates[102] followed six patients with post-treatment biopsy showing mature rhabdomyoblasts. All six patients remained disease-free after a follow-up period of 37 to 237 months. Mature cells with a large smooth solitary nucleus, no significant pleomorphism, no mitotic activity, and the absence of clusters of cells suggestive of growth from a common precursor are the essential features of the diagnosis.[102] Failure of the diagnosis of mature rhabdomyoblasts after apparent tumor cell maturation on biopsy specimen has been reported, but the question of sampling error always exists.[103]

More recently, slides and pathology reports from 44 patients with bladder/prostate rhabdomyosarcoma treated during IRS IV were reviewed to evaluate the significance of rhabdomyoblasts.[104] Of 10 patients with only mature rhabdomyoblasts at their last procedure, only 1 recurred versus recurrence in 4 of 17 patients with viable tumor and 2 of 17 patients with no tumor.[104] Growing evidence supports the conservative management of patients with mature rhabdomyoblasts after treatment, but careful radiologic and endoscopic surveillance should be maintained.

Treatment

New protocols have been developed by the IRS/COG. A broad overview highlighting principles of chemotherapy and radiation therapy follows.

Low-Risk Group

The low-risk group includes patients with localized embryonal tumors occurring at favorable sites (stage I), including botryoid rhabdomyosarcoma (groups I, II, and III), and patients with embryonal tumors located at unfavorable sites who have completely resected disease or only microscopic residual disease. Current protocols attempt to reduce the cumulative doses of cyclophosphamide in this population to limit toxicity. The low-risk group would be divided into two subsets based on stage, location, and clinical group. Patients treated in both subsets would receive vincristine, actinomycin-D, and cyclophosphamide (VAC) for a total of four cycles with diminished doses of cyclophosphamide. Patients in subset 1 would go on to receive another four cycles of actinomycin-D and vincristine (V), whereas patients in subset 2 would continue V for another 12 weeks. Radiation therapy would be given at week 13. Timing of radiation continues to be a controversial subject in patients with rhabdomyosarcoma.

Intermediate-Risk Group

The intermediate-risk group includes patients with embryonal tumors occurring at unfavorable sites (i.e., bladder/prostate), patients with gross residual disease (group III), patients with metastatic embryonal rhabdomyosarcoma who are younger than 10 years, and patients with nonmetastatic alveolar or undifferentiated sarcoma. In this group, the likelihood of bladder preservation decreases to 25% to 45% based on IRS II and IRS III data. Complete resection at the initial procedure is typically impossible.

In the current protocol, irinotecan is combined with vincristine in a randomization arm. Irinotecan belongs to a newer class of chemotherapeutic agents (topoisomerase I inhibitors) and has shown promise in phase I studies.[105,106] Patients in the intermediate-risk group would be randomly assigned to receive VAC alone or VAC alternating with vincristine/irinotecan for 43 weeks of therapy. Local radiotherapy would be initiated in both treatment arms at week 4 based on data from prior IRS protocols indicating improved local control with earlier radiotherapy. At week 13, additional local control can be performed for patients who can safely undergo delayed primary excision.

High-Risk Group

The high-risk group consists primarily of patients with alveolar and undifferentiated rhabdomyosarcoma and patients older than 10 years with embryonal tumors and metastatic disease. Because of the historically poor response to chemotherapy by high-risk patients, the next protocol is expected to combine VAC cycles with interval-compressed multiagent chemotherapy. Specifically, patients would receive interval-compressed cycles of vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide. Patients also would receive an up-front window of vincristine/irinotecan to assess further the response of this combination in previously untreated high-risk patients. Irinotecan also would be used in conjunction with radiotherapy, as a radiosensitizer. Tolerability and toxicity of this combination have not been studied previously in children and would be assessed in this study at weeks 19 to 23.

Late Effects

Patients treated for bladder prostate rhabdomyosarcoma, similar to patients with Wilms' tumor, are at risk for the systemic late effects associated with chemotherapy and radiation therapy. The apparent preliminary success of bladder preservation has drawn particular attention to late effects related to genitourinary tract function.

Mechanisms of Bladder Injury

Surgery, chemotherapy, and radiation therapy all may individually cause bladder dysfunction. Partial cystectomy results in diminished storage capacity. Partial cystectomy can also adversely effect innervation, however, and function of the bladder.[107,108]

Oxazaphosphorine-alkylating agents (i.e., cyclophosphamide) have been associated with hematuria, fibrosis, and bladder contracture. The incidence of these complications is dose-dependent and approaches 40%.[109] Bladder toxicity is due to excretion of acrolein, a toxic metabolite of alkylating agents.[110] Hydration and catheter drainage decrease the incidence of side effects.[111] Mercaptoethane sulfonate (mesna) binds to acrolein, forming a nontoxic stable thioester in the urine, and is routinely used today.[112,113]

Radiotherapy is likely a significant contributor to post-treatment bladder dysfunction. In the series by Yeung and colleagues,[114] only the four children who did not receive radiation had normal bladder function. Similarly, Raney and associates[115] noted that 13 of 43 patients receiving radiation had bladder dysfunction compared with 1 of 9 nonirradiated patients. Hays and associates[116] reported that 9 of 19 irradiated patients had long-term bladder sequelae versus 1 of 11 treated without radiation. A dose effect was suggested in this study: 1 of 6 patients receiving less than 40 Gy had dysfunction as opposed to 8 of 13 receiving more than 40 Gy.[116]

Radiation injury can be classified as acute and long-term. Acute injury is characterized by an inflammatory response within the bladder wall that reduces bladder storage capacity. Acute injury is typically reversible.[117-119] The severity of acute effects depends on the total dose and the fractionation schedule of the radiation applied.[120-124]

The severity of late effects is related to radiation dosage and may include symptoms such as urgency, frequency, hematuria, and diminished bladder compliance.[125] Fibrosis results from collagen deposition in the muscle and subepithelial layers of the bladder wall. Increased transforming growth factor-β expression resulting in altered collagen deposition has been implicated.[126] Radiation-induced interleukin-1 or tumor necrosis factor may trigger increased production of transforming growth factor-β within the bladder.[127-129] Modulation of transforming growth factor-β levels or its precursors could limit bladder dysfunction, but agents for this purpose are not yet available. Other potential solutions include better radiation targeting and the use of brachytherapy.[130]

Success of Bladder Preservation Strategies

With up-front chemotherapy, radiotherapy, and conservative surgery, bladder retention is possible in approximately 60% of patients.[116,131,132] More recent reviews call into question the function of these preserved bladders, however. Objective data are lacking regarding bladder function in children treated for rhabdomyosarcoma.[133] To date, only one small study has used the "gold standard" (urodynamics) to investigate bladder function in these children.

Yeung and colleagues[114] evaluated bladder function in 11 children with tumors involving the bladder base or prostate or both (6), the pelvic wall (2), the vagina (2), and the bladder dome (1).[114] After a mean follow-up of 6.6 years, only 4 of the 11 children had a normal voiding pattern. All of the children who were irradiated had nocturnal enuresis, continuous dribbling, an abnormal bladder capacity, or abnormal voiding. In addition, four of the children displayed evidence of upper tract dilation, and two went on to require surgery. Four children had urodynamic studies completed. All four cases displayed a reduced functional bladder capacity. Only one child had decreased bladder compliance.

Arndt and coworkers[134] reported the outcomes of patients with bladder preservation rhabdomyosarcoma treated during IRS IV (1993-1997). Eighty-eight patients with bladder preservation rhabdomyosarcoma were identified. Seventy percent of these tumors arose from the bladder. Overall 6-year survival was 82%; however, event-free survival was 77% at a mean of 6.1 years follow-up. Of 55 patients who retained their bladders, only 36 (40%) had "normal" bladder function. Urodynamics and standardized questionnaires were not used, suggesting that the true extent of dysfunction may be greater.[135]

More recently, the International Workshop reported on the late effects in 164 patients undergoing treatment for bladder/prostate rhabdomyosarcoma.[136] After biopsy only, 48% of patients had an intact bladder. Of patients 6 years old or older, 31% had urinary incontinence; 27% of patients who had undergone partial cystectomy had similar complaints. Fifty-five percent of patients had recurrent urinary tract infections, 40% had decreased renal function, and 25% had hematuria.[136]

Soler and colleagues[137] presented data on eight children undergoing treatment. Three patients (37.5%) were asymptomatic and had normal urodynamic studies, and another patient had dysuria (this patient went on to continent urinary diversion with transverse colon). The other four patients had urologic complaints, and their urodynamic findings included reduced bladder capacity in four, overactivity in two, urgency in three, and suprapubic pain during filling.

There is a paucity of objective data regarding bladder function in patients treated for bladder/prostate rhabdomyosarcoma. Although many authors have reported reasonable bladder function after therapy, objective analysis with urodynamics, standardized questionnaires, or imaging has not been performed.[138-140] This question is central to determining the effectiveness of current treatment strategies.

REFERENCES

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CHAPTER 50

WILMS' TUMOR

Mohan S. Gundeti

Wilms' tumor (nephroblastoma) is the most common primary malignant solid renal tumor of the kidney in childhood. The incidence rate in the United Kingdom is 7 per 1 million children, accounting for approximately 80 to 90 cases each year. In the United States, the incidence is similar with 8.1 cases per 1 million children accounting for 450 to 500 cases each year.[1]

Since the first description of Wilms' tumor by Wilms in the 18th century, the first nephrectomy by Jessop[2] in 1877, and the addition of radiotherapy in 1915, there have been many advances in the treatment of this tumor, especially in the latter part of the 20th century. The chemotherapeutic agent actinomycin was added in 1953 by Farber and colleagues,[3] and vincristine was added in 1963 by Sutow and coworkers.[4]

Wilms' tumor is an ideal example of the progress made by a multidisciplinary team (i.e., surgeon, oncologist, geneticist, and pathologist) working toward a single goal—improving survival of these children. The introduction of trials by the International Society of Pediatric Oncology in Europe (SIOP) and the National Wilms' Tumor Study (NWTS) in the United States has been extremely beneficial in treatment guidelines and strategies. These trials have resulted in an overall improved survival rate and reduced morbidity compared with previous survivals rate of 15% with surgery alone[5] and 40% with surgery and radiotherapy.[6] Present and future work is directed toward finding new therapeutic strategies for high-risk patients, reducing the therapy for low-risk patients, and studying the new biologic parameters of the tumor.

EPIDEMIOLOGY

Tumor occurrence is almost equal in boys and girls, with a slightly higher predominance in girls in the United States.[7] The median age of presentation is 40 months (3.5 years), and the tumor is seen until age 5 to 6 years. Most tumors at presentation are unilateral; about 5% to 6% are bilateral. Bilateral tumors are especially common in girls with an earlier age of presentation (28 months).[8] There is some ethnic variation in the incidence, with lower reported rates in east Asia compared with the United States and Europe.[7] Familial Wilms' tumor occurs in 1% to 2% of all cases.[9]

HIGH-RISK FACTORS AND ASSOCIATED SYNDROMES

Wilms' tumor usually develops in otherwise healthy children, but in about 8% cases, there are recognized malformations.[10,11] These associated syndromes can be divided into overgrowth and non-overgrowth syndromes (Table 50-1). Beckwith-Wiedemann syndrome is a classic example of an overgrowth syndrome, characterized by excessive overgrowth at the cellular and organ levels (macroglossia, nephromegaly, and hepatomegaly), and hemihypertrophy (Fig. 50-1A). The characteristic clinical features are neonatal hypoglycemia, exomphalos, macroglossia, high birth weight, and gigantism. In addition to Wilms' tumor, these children are at risk of adrenal and hepatic malignancies.[12] The nephromegaly in this spectrum is a high-risk factor for the development of Wilms' tumor. Hemihypertrophy, another common overgrowth syndrome occurring either in isolation or in association with Beckwith-Wiedemann syndrome, is also a risk factor (Fig. 50-1B). Perlman syndrome (visceromegaly, macrosomia, polyhydramnios, and abnormal facies) and Sotos syndrome (macrocephaly, developmental delay) are other rare overgrowth syndromes associated with Wilms' tumor. Nephroblastomatosis is a common feature of Perlman syndrome.[13]

The important non-overgrowth syndromes are WAGR (*W*ilms' tumor, *a*niridia, *g*enital anomalies, and mental *r*etardation) syndrome and Denys-Drash syndrome. Isolated aniridia is also a risk factor for the development of Wilms' tumor. Denys-Drash syndrome is a syndrome associated with Wilms' tumor with male pseudohermaphroditism and glomerulosclerosis leading to nephropathy. Trisomy 18 also is reported to be a risk factor.

The most common genitourinary anomalies associated with Wilms' tumor are hypospadias and undescended testis in about 4%.[14] Other reported associations are horseshoe kidney, pigmented nevi, and neurofibromatosis.

GENETICS OF WILMS' TUMOR

The theory proposed by Knudson and Strong,[15] the loss of tumor-suppressor gene leading to the tumor, strongly correlates to the Wilms' tumorigenesis. Various chromosomal loci have been found to be responsible for Wilms' tumor formation.

WT1 (11p13)

WT1 gene is usually expressed in the developing genitourinary tract and has been detected in the developing kidney at 20 weeks of gestation; it is rarely found in adults. This pattern suggests its importance in the role of renal development and differentiation. Abnormal expression, lack of expression, or deletion usually leads to Wilms' tumor. The exact location of this gene is on short chromosome 11 at the p13 position. This abnormality of *WT1* is associated with WAGR syndrome[16] and Denys-Drash syndrome.[17]

WT2 (11p15)

An excess of material on the chromosome as an extra band at 11p15 in the *WT2* gene coding for insulin-like growth factor has been found. This excess material is responsible for the overgrowth as seen in hemihypertrophy and Beckwith-Wiedemann syndrome.[18]

Other Chromosomal Abnormalities

Abnormalities at chromosomes 17 q12-21,[19] 16q1p,[20] 7p,[21] and p53 in anaplastic tumor[22] have been found.

TUMORIGENESIS (TUMOR FORMATION) AND NEPHROBLASTOMATOSIS

Abnormal collections of blastemal cells are found in about 1% of kidneys on postmortem examination, yet these are found in approximately 40% of kidneys removed for Wilms' tumor. These histologic abnormalities are found uniformly in the kidneys of children with an inherited susceptibility to Wilms' tumor. When multiple nephrogenic rests are found, or when the presence of rests can be inferred, such as in multicentric or bilateral Wilms' tumor, the condition is described as nephroblastomatosis.[23] Not all nephroblastomatoses develop into Wilms' tumor; most regress or develop into a clinically insignificant benign entity. Detection of these rests is challenging on conventional imaging, and they are found only on extensive histologic search.

Table 50-1 **Syndromes Associated with Wilms' Tumor**

Overgrowth	Non-overgrowth
Beckwith-Wiedemann	Denys-Drash
Hemihypertrophy	WAGR
Perlman	Aniridia
Sotos	

Depending on their location in the kidney, these nephrogenic rests are divided into intralobar rests (i.e., within the lobe of the kidney) or perilobar rests (i.e., at the periphery of the kidney). Perilobar nephrogenic rests are associated with 11p15 (*WT2*): Beckwith-Wiedemann syndrome and synchronous bilateral Wilms' tumor. Intralobar nephrogenic rests are associated with 11p13 (*WT1*): aniridia, Denys-Drash syndrome, and metachronous Wilms' tumor (Fig. 50-2).[24]

PATHOLOGY OF WILMS' TUMOR

On gross specimen, Wilms' tumor has a varied appearance of smooth to cystic and variegated on cut section. There is no distinct capsule, but the surrounding mesenchyme condenses to form a pseudocapsule. Occasionally, hemorrhage and necrosis are noted on gross specimen examination. The whole specimen is handled very carefully, and gross specimen examination, microscopic study, and further biologic studies are performed according to the protocols by SIOP 2002 in Europe and the American College of Pathologists in the United States.[25]

For macroscopic examination, the tumor should be send to the pathology department intact without formalin preservative. The examination includes specimen weight, tumor location, capsule invasion, renal vein and sinus invasion, ureter, and cut surface of the kidney if a heminephrectomy was performed.

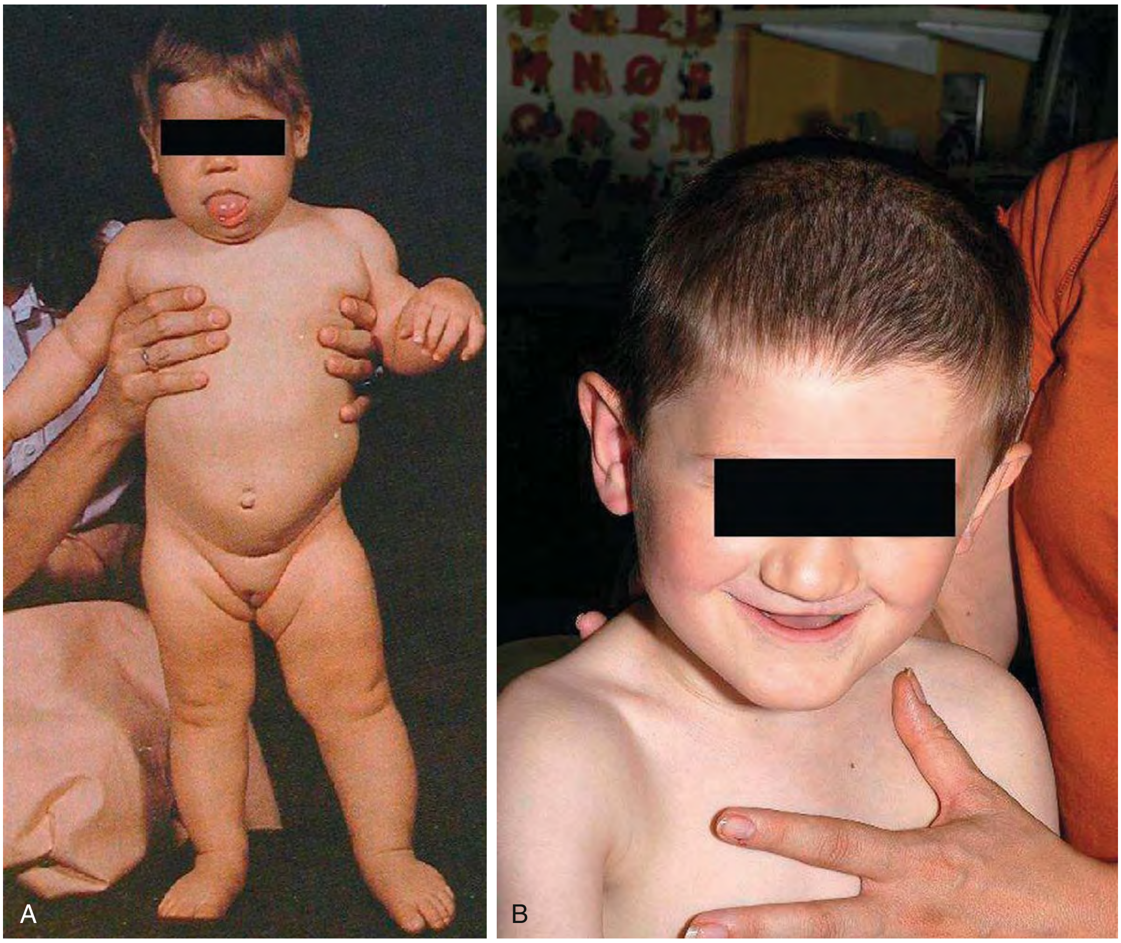


Figure 50-1 **A,** Beckwith-Wiedemann syndrome in high-risk syndromes. **B,** Isolated hemihypertrophy in high-risk syndromes. (**A,** Courtesy of Mr. D. T. Wilcox.)

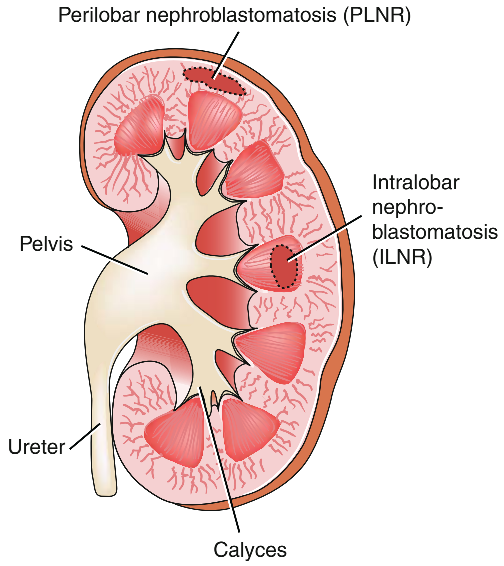

Perilobar nephroblastomatosis (PLNR)
Intralobar nephro- blastomatosis (ILNR)
Pelvis
Ureter
Calyces

Figure 50-2 Location of various types of nephroblastomatosis.

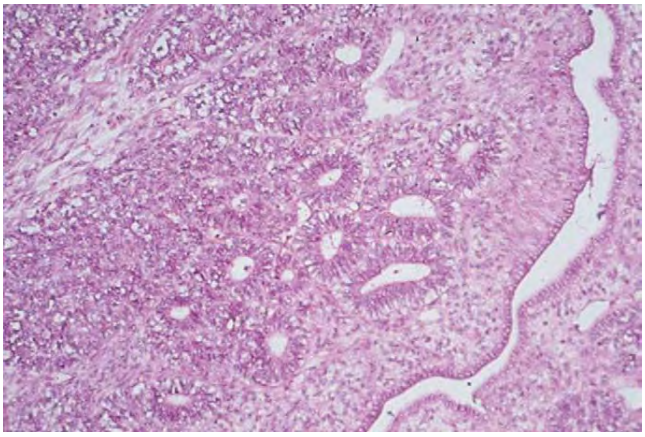


Figure 50-3 Favorable-histology Wilms' tumor.

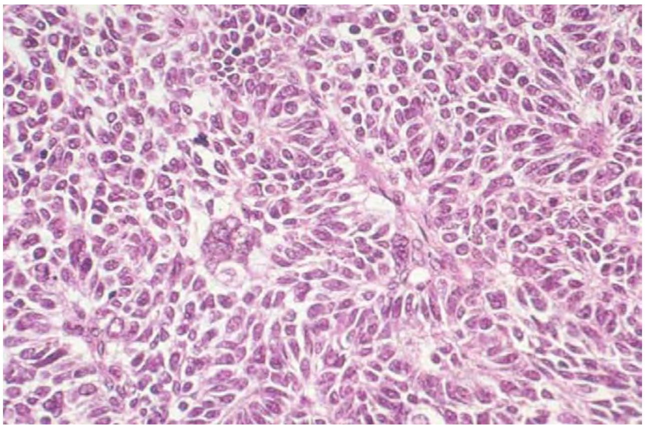


Figure 50-4 Histology of diffuse anaplastic variety Wilms' tumor.

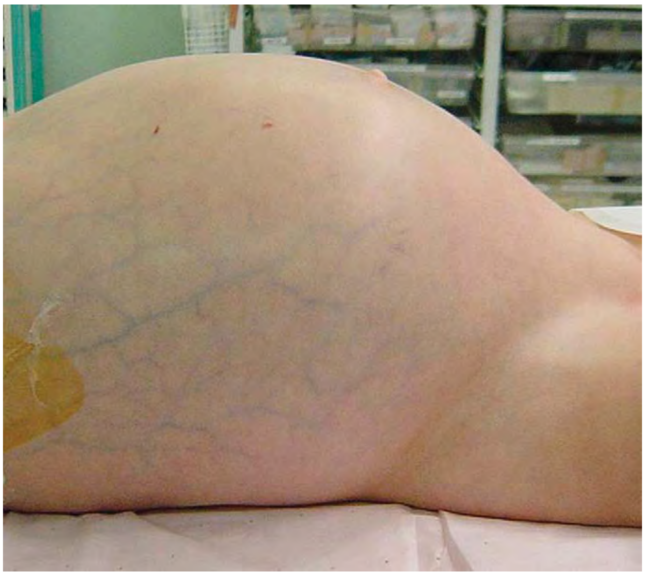


Figure 50-5 Abdominal distention owing to a large tumor.

The most vital thing on pathologic examination, apart from staging, is to classify the tumor into favorable-histology and anaplastic tumor because this is the key factor for prognosis and further treatment. Classic favorable-histology Wilms' tumor, also called triphasic Wilms' tumor, has three components: blastemal, stromal, and epithelial. Occasionally, other embryonic cells, such as skeletal, squamous, or cartilage, are found. Perilobar nephrogenic rests resemble these microscopic findings, and the distinction is made by the absence of a peritumoral fibrous capsule in a perilobar nephrogenic rest (Fig. 50-3).

Anaplasia refers to gigantic polypoid nuclei with increased chromatin content and the presence of multipolar mitotic figures.[25] The anaplasia may be focal or diffuse depending on location. This feature is uncommon; it is found in about 5% to 10% of the total Wilms' tumor population (Fig. 50-4).[26] Most tumors are unicentric; 7% to 10% are multicentric.

PRESENTATION

A clinically palpable, painless abdominal mass in an otherwise healthy child is the most common presentation (Fig. 50-5). Often, a child may present with only constitutional symptoms, such as fever and malaise. Sometimes the presentation includes hematuria and pain. Pain is usually rare, and it may indicate tumor rupture; this is associated with hypotension and anemia.[27,28] The clinical spectrum mimics an acute abdomen. Hypertension is occasionally found, probably related to the increased renin formation,[29] or compression effect of the tumor on vascular structures.

If the tumor extends into the inferior vena cava (10% as reported by NWTS),[30] this may result in bilateral lower limb edema and varicocele in a boy. Hepatic vein obstruction leads to hepatomegaly and ascites. The tumor thrombus extending into the atrium has rarely resulted in congestive heart failure. Lung metastasis may manifest with recurrent respiratory tract infection or a pleural effusion[31] with cough. The clinical examination should look at all of these aspects and should specifically look for the signs of associated syndromes as mentioned earlier.

EXTRARENAL WILMS' TUMOR

Extrarenal Wilms' tumor is rare but often noted. The presence of ectopic metanephric blastemal cells or the *Wt* gene that causes transformation of extrarenal primitive mesonephric

Table 50-2 Differential Diagnoses of Renal Tumor in Childhood

Benign	Malignant
Renal abscess	Nephroblastoma
Multicystic kidney	Neuroblastoma
Multilocular cyst	
Xanthogranulomatous pyelonephritis	

remnants into Wilms' tumor during embryogenesis is considered the cause. These tumors are located in the retroperitoneum,[32] in the uterus, in the cervix, in the pelvis, along the line of spermatic cord testes, and in the thorax. The histologic characteristics are the same.

EVALUATION, INVESTIGATIONS, AND IMAGING OF TUMOR

The aim of the evaluation is a preoperative diagnosis, staging, and assessment of the vascular anatomy and surrounding organs from the surgical aspect and to rule out bilaterality of the tumor (Table 50-2). The initial simple workup includes complete blood count, renal biochemistry, and coagulation studies because acquired von Willebrand's disease is known in 8% of patients.[33] Urinalysis for proteins and catecholamines is performed to rule out neuroblastoma.

Ultrasonography

Ultrasound scan is the initial fast noninvasive test to help to distinguish between a cyst and tumor, and to detect small tumor in the opposite kidney or liver and abdominal metastasis. Ultrasound with Doppler also detects inferior vena caval patency. The SIOP protocol places emphasis on three-dimensional measurement of the tumor on ultrasound scans. The challenge with ultrasound is differentiating the nephrogenic rests from tumor. The nephrogenic rests are usually ovoid, static, superficial, and multiple compared with tumor, which is rounded, expanding, deeply situated, and solitary.

Computed Tomography Scan of Abdomen and Pelvis

Computed tomography (CT) provides cross-sectional imaging to help in identifying the renal origin of the tumor, extent, regional nodes, and surrounding organ involvement. Inferior vena caval thrombus is also clearly seen. The more recent sophistication in CT scanners and awareness among radiologists have been effective in reducing the radiation dosage. Plain and contrast images are important to see the details of the tumor and vascular anatomy. Contralateral kidney anatomy is also assessed for small lesions (Fig. 50-6).

Chest Radiograph

Posteroanterior and lateral radiographic views to detect pulmonary metastasis are mandatory. The chest radiograph has limitations in detecting micrometastasis, however. Most centers prefer performing a CT scan of the chest at the same time as the abdomen, which may be more convenient and specific for the detection of metastasis.

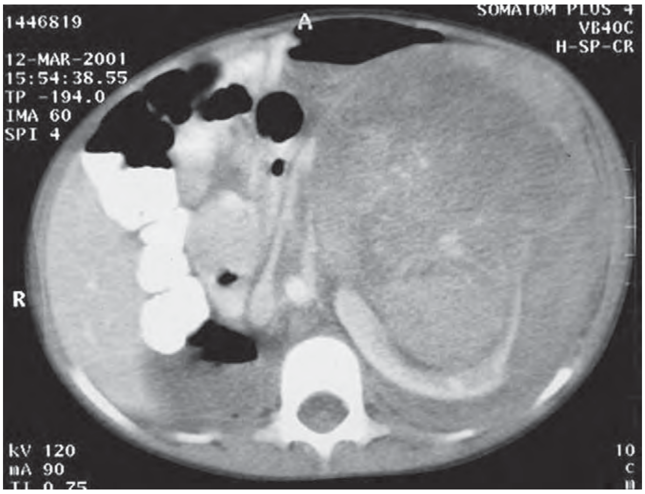


Figure 50-6 CT scan of left Wilms' tumor.

Magnetic Resonance Imaging

When involvement of the inferior vena cava is suspected, magnetic resonance imaging (MRI) is the best way of mapping intravascular extension.[34] The other advantage of MRI is that it also differentiates thrombus involvement in the lumen from the vascular wall (Fig. 50-7).

Echocardiography

Echocardiography is performed to detect the intra-atrial extension of the tumor thrombus, which was found in 20% of children with thrombus. Echocardiography is also mandatory before starting doxorubicin (Adriamycin) as part of chemotherapy in high-risk children.

Positron Emission Tomography

Positron emission tomography (PET) with the glucose analog fluorodeoxyglucose is a recent addition to the imaging armamentarium and is still under review. PET detects the primary tumor and metastases. In a more recent review, a combination of PET with CT scan was superior in staging for solid tumors in adults.[35]

Bone Scan and Brain Magnetic Resonance Imaging

Bone scan and brain MRI are performed in clear cell sarcoma of the kidney and rhabdoid tumor of the kidney.

Imaging of Bilateral Renal Tumors

In addition to the above-mentioned imaging, a dimercaptosuccinic acid radioisotope renal scan is mandatory to evaluate the split renal function. In selective cases, arteriography or MR angiography is important to delineate the renal arterial anatomy before partial nephrectomy or bench surgery.

STAGING OF WILMS' TUMOR

Staging is crucial in the management of Wilms' tumor because treatment and prognosis depend on accurate staging. NWTS staging is based on the surgical and histopathologic findings (Table 50-3). Lymph node sampling is important to

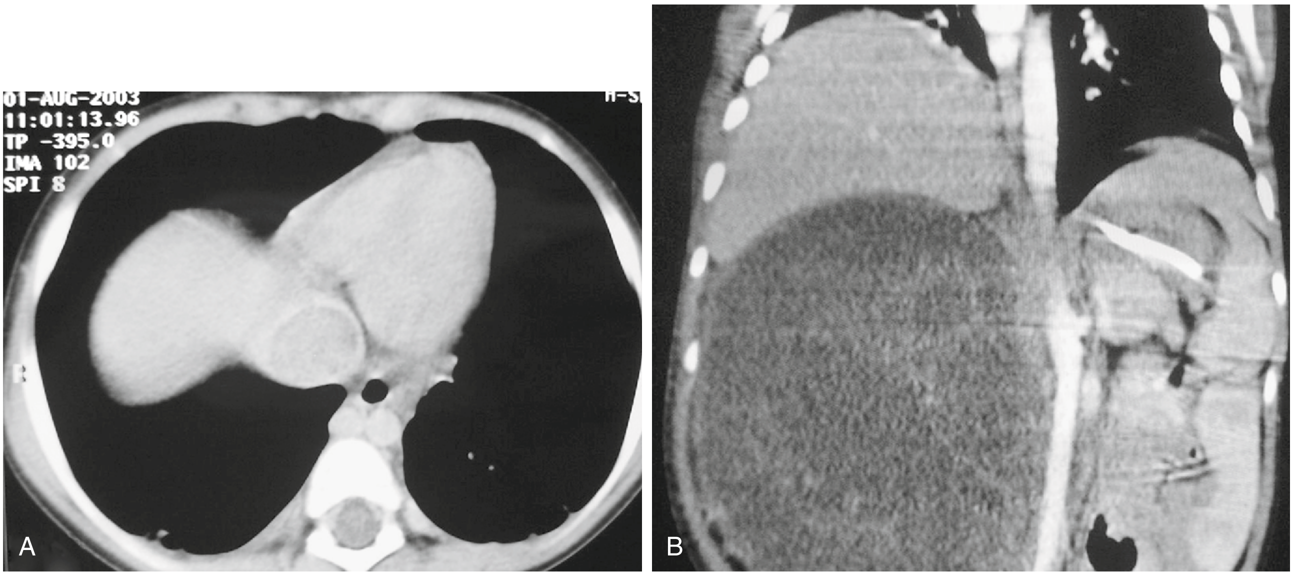


Figure 50-7 **A,** CT scan showing inferior vena cava thrombus. **B,** MRI scan showing inferior vena cava thrombus with tumor.

accurate staging. Complete nodal clearance is not needed. The distribution of tumor according the NWTS-4 study group was as follows: stage 1, 41.8%; stage 2, 27.5%; stage 3, 21.5%; and stage 4, 9.3%.

MANAGEMENT OF WILMS' TUMOR

Management consists of surgery for removal of the primary tumor with the kidney (radical nephrectomy), with chemotherapy and radiotherapy in some cases. The management is guided by the NWTS protocol in the United States and the SIOP protocol in Europe according to the stage of the tumor.

Surgery

Radical nephrectomy for removal of the primary tumor with the kidney is the mainstay of treatment. This procedure allows the removal of the primary tumor and accurate staging of the tumor. The usual approach is transperitoneal through a transverse abdominal incision, which gives good access to the tumor and vasculature.

The principles of surgery are as follows:

1. Palpation of liver, abdomen, and para-aortic region for regional spread of disease
2. Removal of intact specimen in total
3. Avoidance of local spillage because these children have a sixfold increase in local abdominal relapse[36]
4. Nodal sampling rather than clearance because there is no added advantage in the long-term survival[37]
5. Proper identification and avoidance of injury to contralateral renal vessels, aorta, and iliac and superior mesenteric arteries[38]
6. Palpation of the renal vein and inferior vena cava before ligation to rule out thrombus

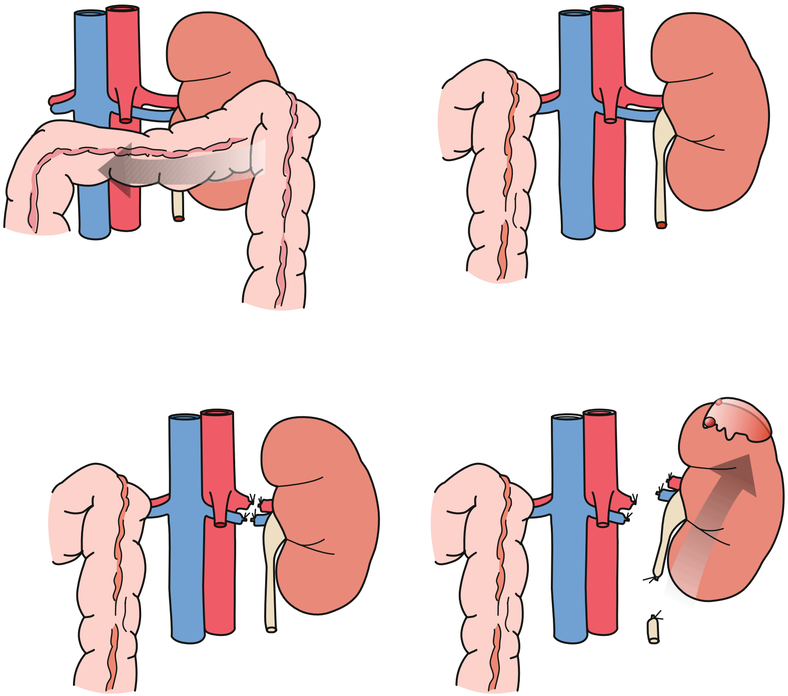
Exploration of Contralateral Kidney

In the past, careful examination of the contralateral kidney as a part of the exploratory laparotomy was widely accepted, but not always done. This was done at the outset to rule out the potential bilaterality of the tumor. Modern imaging techniques (CT and MRI) are much more likely to identify the intrarenal tumor than palpation with the surgeon's hand. Palpation of the contralateral kidney is mandatory according to NWTS, however, because there have been reports of missed bilateral cases despite imaging: in 0.3% of 3335 registered cases, but the outcome was not affected.[39]

Table 50-3 National Wilms' Tumor Study Staging of Wilms' Tumor

Stage 1	Tumor limited to kidney and completely resected. Renal capsule intact. Tumor not ruptured or biopsied before removal. No residual tumor beyond margins of resection
Stage 2	Tumor extends beyond kidney, but completely resected. Regional extension of tumor (vascular invasion outside renal parenchyma or capsular penetration with negative excision margin). Operative tumor spill confined to flank (no peritoneal contamination). Tumor biopsy (except fine-needle aspiration) before surgery
Stage 3	Nonhematogenous metastases confined to the abdomen (e.g., tumor in regional lymph nodes) including tumor implants on or penetrating the peritoneum. Gross or microscopic tumor remains postoperatively. Tumor spill before or during surgery not confined to flank. Piecemeal excision of the tumor (removal in >1 piece)
Stage 4	Hematogenous metastasis or lymph node metastases outside the abdominopelvic region (beyond renal drainage system, e.g., lung and liver)
Stage 5	Bilateral renal involvement at diagnosis (each side should be staged separately, according to above criteria, as stage 1-4)

From Qualman SJ, Bowen J, Amin MB, et al. Protocol for the examination of specimen from patients with Wilms' tumor or other renal tumors of childhood. *Arch Pathol Lab Med.* 2003;127:1280-1289.



Surgical Steps

After initial palpation of the abdomen, the colon is reflected and moved completely away from the kidney. Major vessels (i.e., aorta, inferior vena cava, renal artery and vein, superior mesenteric artery) are identified. Mobilization of the tumor toward the surgeon helps in exposure of the renal hilum. Renal vessels are ligated after confirmation. The ureter is divided, and the specimen is removed in total. The adrenal may not need to be removed if it is clearly away from the tumor (Fig. 50-8).

The vessels most at risk during excision of a right renal tumor are the vena cava and left renal vein (Fig. 50-9). During removal of a left renal tumor, the vessels at risk are the aorta, superior mesenteric artery, and right renal artery.

Surgery in Tumor with Caval Thrombus

After confirmation of imaging in regard to the superior extension, a proper surgical approach is decided. For thrombus extension, up to retrohepatic level as a good control of the vena cava above and below the thrombus level allows complete removal of the thrombus. Suprahepatic level and extension into the atrium, where a superior control is impossible, needs a cardiac bypass (extracorporeal circulation) team with a cardiothoracic surgeon. These children have chemotherapy before surgical intervention. Occasionally, the tumor may be adherent or involve the inferior vena cava, and cavectomy may be performed safely.[40]

Surgical Complications

NWTS has reported a surgical complication rate of 11% for primary nephrectomy.[41] Common complications were hemorrhage and small intestinal obstruction. Other complications are intussusception and damage to adjacent organs. The cause of intestinal obstruction in the immediate postoperative period is mostly intussusception. Risk factors identified were higher local tumor stage, intravascular extension, and en bloc resection of other visceral organs.

Laparoscopic Approach

In a more recent report,[42] the primary nephrectomy was performed by a transperitoneal approach after preoperative chemotherapy. There are no randomized control studies looking at the beneficial role of this approach.

Primary Nephrectomy (NWTS) and Neoadjuvant Chemotherapy Followed by Nephrectomy (SIOP)

According to the NWTS protocol, following confirmation on imaging, the nephrectomy is performed enabling the collection of tissue for histologic diagnosis, primary removal of the tumor, and exact staging. This surgery is often challenging, however, in view of the tumor size and the need to adhere to strict principles of surgery, especially regarding intraoperative tumor spilling.

According to the SIOP protocol, after imaging of the tumor, a fine-needle biopsy is performed to obtain a histologic diagnosis. Under the same anesthesia, vascular access (Hickman line) is obtained for administering the chemotherapy. After 4 weeks of chemotherapy, the response is assessed by repeat ultrasound scan, and nephrectomy is performed on week 5 or 6 (SIOP-9 2001). The potential advantage is that the tumor is small, and the risk of intraoperative spillage is reduced.[43] According to the UKW3 study group, this approach has also resulted in a shift toward a more advantageous stage distribution and reduction in therapy and late effects of doxorubicin and radiotherapy.[44] The disadvantage is that studying tumor specimen histology after chemotherapy may not be the same as the NWTS protocol, especially nodal histology for defining postoperative chemotherapy.

Postoperative Further Treatment

Depending on imaging, operative and histologic staging in NWTS, and postchemotherapy nephrectomy with intraoperative findings by SIOP, further treatment is decided in individual cases.

NWTS Protocols

NWTS was established in 1969 to determine treatment protocols to improve the survival and reduce the toxicity of adjuvant treatment. Over the last 40 years, the treatment has evolved with individual stages of the study, the current stage being NWTS-5.

NWTS-1 (1969-1973)

During NWTS-1, 606 patients were included in the study group. The conclusion was that postoperative radiotherapy is effective for selected patients. The combination of vincristine and actinomycin D is more effective than either drug alone. There is no evidence for a role for preoperative vincristine, but numbers were too small to be conclusive.[45]

NWTS-2 (1975-1978)

For NWTS-2, 775 patients were included in the study group. The conclusion was that there is no indication that prolonged postoperative chemotherapy is of any value. Doxorubicin is an effective drug in Wilms' tumor. NWTS-2 has also allowed refinements in the staging system and identified that lymph node positivity is a poor prognostic factor on survival.[46]

NWTS-3 (1979-1985)

For NWTS-3, 2495 patients were studied. The conclusion was that in low-stage tumors postoperative chemotherapy could be reduced further. Radiotherapy, if necessary, does not have to be high dose. Doxorubicin adds to the effect of the vincristine and actinomycin D combination. Addition of cyclophosphamide does not improve survival.[47]

NWTS-4 (1986-1994)

In NWTS-4, 905 previously untreated children were randomly assigned for duration of treatment or for single dose versus divided dose of drug administration. The aim was to evaluate the efficacy, toxicity, and costs of the administration of different regimens for the treatment of Wilms' tumor. The conclusion was that 6-month treatment was more effective than 15-month treatment with lower cost of treatment.[48]

NWTS-5

The aim of NWTS-5 is the evaluation of biologic prognostic factors on tumor specimens to predict the risk of relapse (e.g., 16q1p),[20] which would allow a reduction in the amount of therapy for low-risk patients, while maximizing therapy for high-risk patients (Table 50-4).

Indications of Preoperative Chemotherapy for Wilms' Tumor (NWTS)

As discussed earlier, primary nephrectomy is performed according to the NWTS protocol, but there is a role for preoperative chemotherapy in patients with the following conditions:

1. Inoperable tumor at the primary nephrectomy because removal of surrounding organs can result in an increased risk of surgical complications[49]
2. Inferior vena cava thrombus, especially the suprahepatic level, reducing the need for cavotomy and cardiopulmonary bypass as per NWTS and UKW3 trial[50,51]
3. Bilateral tumor at the diagnosis or incidental finding, at the primary nephrectomy[52]

International Society of Pediatric Oncology

This SIOP treatment guideline is followed in most of Europe. A good collaborative multidisciplinary team has determined the protocols over several years to improve the survival of Wilms' tumor patients.

Table 50-4 Postoperative Treatment Protocol (after Nephrectomy) According to National Wilms' Tumor Study–5

	Radiotherapy	Chemotherapy
Stage 1, 2 FH	None	EE-4A: pulse-intensive AMD plus VCR (18 wk)
Stage 1 anaplasia	1080 cGY*	DD-4A: pulse-intensive AMD, VCR, and DOX (24 wk)
Stage 3, 4 FH		
Stage 2-4 focal anaplasia	Yes†	Regimen 1: AMD, VCR, DOX, CPM, and etoposide
Stage 2-4 diffuse anaplasia		
Stage 1-4 CCSK	Yes†	Regimen RTK: carboplatin, etoposide, and CPM
Stage 1-4 RTK		

*Stage 4 FH—patients are given radiation based on the local tumor stage.
†Radiation therapy is given to all patients with CCSK and RTK; consult protocol for specific treatment.
AMD, actinomycin D; CCSK, clear cell sarcoma of the kidney; CPM, cyclophosphamide; DOX, doxorubicin; FH, favorable histology; RTK, rhabdoid tumor of the kidney; VCR, vincristine.

SIOP-1 (1971-1974)

In SIOP-1, 398 patients were studied, and the conclusion was that prenephrectomy radiotherapy reduces the number of tumor ruptures and produces a more favorable stage distribution after surgery. Postoperative prolonged administration of actinomycin D does not contribute to better disease-free survival.[53]

SIOP-2 (1974-1976)

In SIOP-2, 138 patients were studied to confirm the findings of SIOP-1 without randomization. The conclusion was that there was no need for a two-drug combination (vincristine and actinomycin D) to be given for more than 9 months in the postoperative period.

SIOP-5 (1977-1979)

In SIOP-5, 433 patients were randomly assigned for preoperative chemotherapy with vincristine/actinomycin D and radiotherapy. The conclusion was that chemotherapy is comparable to radiotherapy in regard to tumor rupture or stage distribution during the nephrectomy.[54]

SIOP-6 (1980-1987)

In SIOP-6, 1095 patients were enrolled in this study, which answered the following questions:

1. After preoperative chemotherapy and surgery, 17 weeks of postoperative chemotherapy with vincristine and actinomycin D is as effective as 38 weeks in stage 1.
2. The arm looking at the need for postoperative radiotherapy in stage 2 without nodal involvement was prematurely withdrawn because of relapse in cases without radiotherapy.
3. Stage 2 nodal involvement and stage 3 patients had overall better disease-free survival with the addition of doxorubicin.[55]

SIOP-9 (1987-1991)

Of 852 patients in SIOP-9, 382 had eligible localized tumors and were randomly assigned for the duration of the preoperative chemotherapy. At the end of the study, it was shown that 4 weeks of chemotherapy is equivalent to 8 weeks in terms of proportion of stage 1, intraoperative tumor rupture, and 2- to 5-year survival.[56]

SIOP 93-01 (1993-1999)

In SIOP 93-01, 1104 patients were studied to determine the duration of postoperative chemotherapy in stage 1 tumors with intermediate-risk histology or anaplasia. The preliminary results showed that the reduction of postoperative chemotherapy from 18 weeks to 4 weeks in this group is safe.

SIOP 2001

SIOP 2001 is the current ongoing study (Tables 50-5 and 50-6). On the basis of previous SIOP studies, the aims are as follows:

1. Confirm continued use of preoperative chemotherapy for 4 weeks (vincristine and actinomycin D) in stage 1 patients; patients with metastasis at diagnosis would continue to receive chemotherapy for 6 weeks with addition of doxorubicin
2. Perform a multicenter prospective study to find out if doxorubicin is necessary in intermediate-risk tumors and local stage 2 and 3
3. Study specific histologic subtypes in relation to prognosis (e.g., epithelial and stromal dominant are good prognostic factors, blastemal is a poor prognostic factor), studying significance of necrosis in postchemotherapy specimens
4. Minimize acute and late toxicity of therapy without affecting survival in focal anaplasia and intermediate-risk tumors
5. Determine the relationship of tumor volume after chemotherapy and histologic subtypes
6. Establish single-dose actinomycin D as opposed to a fractionated schedule
7. Perform a biologic study to correlate allele loss at 16q1p with relapse-free and overall survival

Treatment of Metastatic Diseases (Stage 4) According to SIOP 2001

Pulmonary Metastasis. If there are micrometastases (<10 mm nodule) on CT scan, but not visible on chest x-ray, the clinician should evaluate after nephrectomy. If repeat CT scan does not show a nodule, the local disease should be treated. If CT scan is positive, and the lesion is resectable, surgery is performed for the excision of the nodule. If the lesion is not resectable, a biopsy specimen is obtained. For viable tumor, chemotherapy according to stage 4 and radiotherapy are indicated.

Liver Metastasis. Stage 4 chemotherapy and radiotherapy are indicated for liver metastasis. If the tumor is resectable, surgery is performed.

Brain Metastasis. For brain metastasis, stage 4 chemotherapy and radiotherapy to the brain are indicated.

Bone Metastasis. Stage 4 chemotherapy and radiotherapy to the lesion seen on imaging (with a margin of ≥3 cm in any direction) are indicated for bone metastasis.

Table 50-5 **Revised International Society of Pediatric Oncology Working Classification of Renal Tumors of Childhood (SIOP 2001)**

For Pretreated Cases	For Primary Nephrectomy Cases
Low-risk tumors	Low-risk tumors
Mesoblastic nephroma	Mesoblastic nephroma
Cystic partially differentiated nephroblastoma	Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma	
Intermediate-risk tumors	Intermediate-risk tumors
Nephroblastoma—epithelial type	Nonanaplastic nephroblastoma and its variant
Nephroblastoma—stromal type	Nephroblastoma—focal anaplasia
Nephroblastoma—mixed type	
Nephroblastoma—regressive type	
Nephroblastoma—focal anaplasia	
High-risk tumors	High-risk tumors
Nephroblastoma—blastemal type	Nephroblastoma—diffuse anaplasia
Nephroblastoma—diffuse anaplasia	Clear cell sarcoma of the kidney
Clear cell sarcoma	Rhabdoid tumor of the kidney
Rhabdoid tumor of the kidney	

Role of Partial Nephrectomy in Unilateral Wilms' Tumor

Partial nephrectomy has been performed for localized disease, especially stage 1 tumors after chemotherapy for small lesions and histologically favorable or intermediate lesions,[57] the aim being to preserve the nephrons and avoid future renal failure. The reported rate of renal failure in NWTS was 0.25%.[58] The risk factor for renal insufficiency in this study was Denys-Drash syndrome, which has inherent renal impairment. There are no randomized studies for partial nephrectomy, and the multicentric nature of the tumor may make this a less than ideal approach. There is probably a role for partial nephrectomy in patients who already have renal impairment; patients with solitary kidney tumors; and patients with high-risk syndromes, such as Beckwith-Wiedemann syndrome, hemihypertrophy, and aniridia, who are at increased risk for metachronous bilateral diseases.

Management of Bilateral Wilms' Tumor

Bilateral tumor constitutes about 5% of all Wilms' tumors. The challenges associated with bilateral Wilms' tumor include optimal control of the tumor and preserving the nephrons. NWTS and SIOP have similar modes of treatment: histologic diagnosis with open surgery (NWTS) or fine-needle biopsy (SIOP) followed by chemotherapy. The response to chemotherapy is assessed by repeat imaging (ultrasound or CT scan) in SIOP, whereas a second-look laparotomy is performed to assess the response in the NWTS protocol.[59] If there is no response, the histology should be reviewed; sometimes a repeat biopsy is needed, or changing the chemotherapeutic regimen needs to be considered (Figs. 50-10 and 50-11).

During the definitive surgery, the kidney with less tumor volume is operated on first, then after an interval, the other side is operated on. If the tumor volume on the contralateral side occupies the whole kidney, a complete nephrectomy with partial nephrectomy on the less affected side is performed at the same time. Surgery consists of partial nephrectomy or occasionally wedge excision or enucleation. The most important aspect of surgery is getting negative margins of the resection and vasculature control. A map of the arterial anatomy guides in the management (Fig. 50-12).

The postoperative treatment depends on the individual side tumor stage and grade. Overall, these children have a good prognosis with survival of 74% with a median follow-up of 52 months.[60] The renal function in the long-term is promising; renal failure was 9.1% in synchronous tumors and 18.8% in metachronous tumors.[58]

Table 50-6 **Summary of Postoperative Treatment Strategies for Localized Tumors (SIOP 2001)**

	Stage 1	Stage 2	Stage 3
Low risk	No further treatment	AV-2†	AV-2
Intermediate risk	AV-1*	DOX + AVD; R < DOX – AV-2‡	RT/DOX + AVD; R < RT/DOX – AV-2‡
High risk	AVD§	High-risk¶ + RT	High-risk¶ + RT

*Regimen AV-1 consists of actinomycin and vincristine for 4 wk.
†Regimen AV-2 consists of actinomycin and vincristine for 27 wk.
‡R< stage 2 and stage 3 intermediate risk is randomized to with (+) and without (–) DOX.
§Regimen AVD consists of actinomycin, vincristine, and doxorubicin for 27 wk.
¶High-risk regimen consists of alternating courses with combination of two drugs, DOX + cyclophosphamide alternating with etoposide+ carboplatin for 34 wk.
DOX, doxorubicin; R, randomized; RT, radiotherapy.

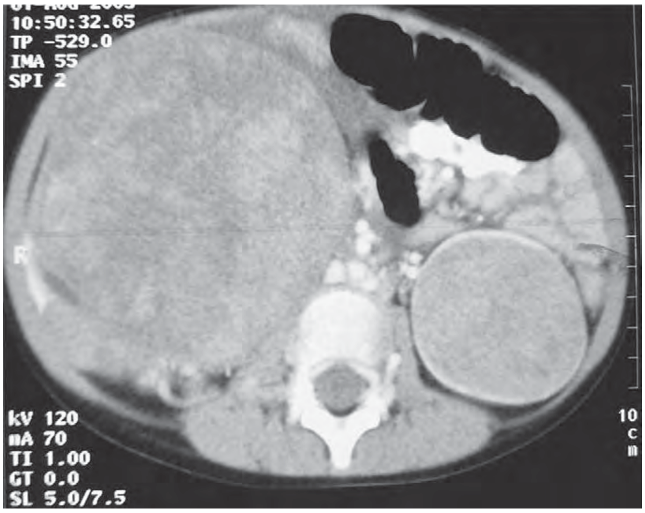


Figure 50-10 CT scan of bilateral Wilms' tumor.

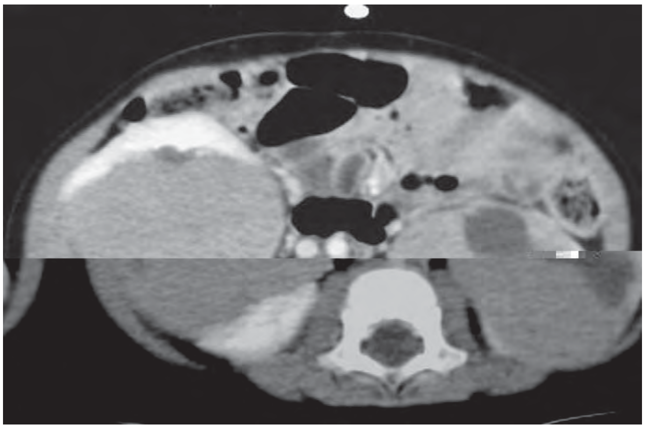


Figure 50-11 CT scan of the same patient with bilateral Wilms' tumor shown in Figure 50-10 after chemotherapy.

Rarely, when partial nephrectomy is impossible on either side because of the tumor volume, bilateral nephrectomy is performed. The child is placed on renal replacement therapy for a 2-year disease-free interval and then transplantation is performed; this allows a metastasis-free interval.[61] Bilateral tumors detected incidentally on exploration should be managed with the above-described plan after biopsy of both sides at the exploration.

Metachronous bilateral tumors refer to tumor arising in the remaining kidney after a complete remission of the unilateral tumor. The treatment protocol is biopsy, chemotherapy, and partial nephrectomy (nephron-sparing surgery).

PROGNOSIS AND SURVIVAL

Staging of the disease is crucial because it determines treatment and survival. The SIOP 93-01 data show approximate 5-year event-free survival rates as follows:

- Stage 1—87%
- Stage 2—85%
- Stage 3—74%
- Stage 4—60% to 70%

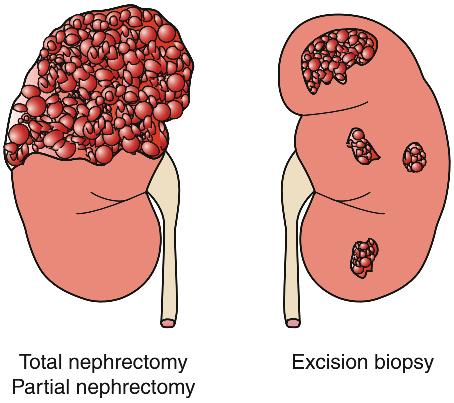


Figure 50-12 Surgical options for bilateral Wilms' tumor depending on the tumor volume. (Courtesy of Mr. P. G. Duffy.)

The favorable-histology tumors have good survival compared with the anaplastic variety. According to NWTS-3, in patients of all stages randomized, the disease-free survival was 86% for favorable-histology tumors and 64% for anaplastic tumors. Although age is not an independent prognostic factor, it has significance in extremes of ages, such as in neonates and adults.

In regard to chromosomal abnormalities, patients with tumor-specific loss of heterozygosity for chromosomes 1p and 16q have a higher relapse rate than patients without loss of heterozygosity.[20] Expression of high levels of telomerase (TERT mRNA, or telomerase RNA template) is associated with a high recurrence rate.[62] DNA flow cytometry, vascular endothelial growth factor, hyaluronic acid, fibroblast growth factor, and serum renin are under study to determine their exact prognostic role and the potential ability to identify recurrence early with these markers (Table 50-7).

The NWTS follow-up protocol is somewhat similar to SIOP. The aim is to detect potential metastasis early and the sequelae of therapy (i.e., radiotherapy and chemotherapy) on various organs.

MANAGEMENT OF NEPHROBLASTOMATOSIS

The characteristic feature of nephroblastomatosis is nonenhancement (homogeneous) with contrast CT and MRI. Wilms' tumor is generally heterogeneous and enhances with contrast CT.

The management of nephroblastomatosis is controversial. A more recent retrospective long-term study of the perilobar hyperplastic variety of Wilms' tumor showed that children who were not treated all developed Wilms' tumor compared with children treated with chemotherapy or surgery. The interval between diagnosis and development of tumor was 13 to 116 months (median 42 months).[63] Children with multifocal nephroblastomatosis in a kidney removed for Wilms' tumor are at an increased risk for contralateral Wilms' tumor and need ultrasound scans every 3 months. If these contralateral tumors are increasing in size during the follow-up period, a local excision (nephron-sparing surgery) should be contemplated. Another report suggested that chemotherapy or local excision (nephron-sparing surgery) for multifocal enlarging nephroblastomatosis is effective.[64]

SIOP 2001 Protocol for Management of Nephroblastomatosis

The SIOP 2001 protocol for management of nephroblastomatosis is as follows:

Table 50-7 **International Society of Pediatric Oncology Recommended Follow-up Investigations on Treatment and off Treatment**

On Treatment	
Chest x-ray	Every 3 mo for localized tumors
	At weeks 6 and 12 and then every 3 mo for metastatic disease
Abdominal ultrasound	At diagnosis (three-dimensional measurement)
	Immediately before nephrectomy (three-dimensional measurement)
	Every 3 mo during treatment
Full blood count	Before each chemotherapy
Serum creatinine	At diagnosis and before each chemotherapy
Liver function test	Before each chemotherapy with AMD or DOX
Blood pressure	At diagnosis and during each visit
Echocardiography	At diagnosis
	Before DOX
	At end of therapy
Renal function monitoring	GFR with ^{51}Cr EDTA before and after every third course of carboplatin
	End of treatment
	In children with renal dysfunction
Off Treatment	
Chest x-ray	Every 3 mo until 3 yr after end of treatment
Abdominal ultrasound	Every 3 mo to age 7 yr if patient was <12 mo old at initial diagnosis, nephrogenic rest on nephrectomy specimen, initial bilateral tumors, partial nephrectomy
	Every 3 mo for 2 years or clinical examination in compliant patients for all other patients
Blood pressure	Annually
Growth	Monitor annually (every 6 mo through puberty)
	Examine for scoliosis
Echocardiography	Every 5 yr if end of treatment study was normal
	If abnormal, more frequently
Renal function monitoring	Every 5 yr (more frequently if renal dysfunction)
	Assess serum urea/electrolytes/creatinine
	Measure urine protein-to-creatinine ratio
	Measure magnesium in high-risk patients or patients treated with carboplatin

AMD, actinomycin D; DOX, doxorubicin; ^{51}Cr EDTA; chromium 51 ethylenediaminetetraacetic acid; GFR, glomerular filtration rate.

1. After diagnosis is established, chemotherapy with vincristine and actinomycin D combination
2. First response assessment after 4 weeks of therapy by ultrasound or CT scan or both; if decrease in tumor size, chemotherapy until complete resolution of lesion
3. Surgery if progression of lesion despite chemotherapy or lesion becomes heterogeneous; partial nephrectomy or wedge excision as in cases of bilateral lesions
4. When lesion has disappeared with chemotherapy or with surgery, maintenance chemotherapy continued for 1 year

HIGH-RISK PATIENTS: RISK OF TUMOR FORMATION AND SCREENING

Screening with ultrasound every 3 months in children with high-risk syndromes is suggested until age 7 years to detect the tumors earlier.[65] The risk of tumor formation in Beckwith-Wiedemann syndrome is 4% to 7%. Beckwith-Wiedemann syndrome is related to the imprinting status of the *H19* and *LIT1* genes on chromosome 11p15. In a meta-analysis, it was found that loss of imprinting of *H19* implies a higher tumor risk—almost 54%.[66] NWTS has reported that these children are noted to have small tumors detected on regular screening. There is also a high risk of bilateral diseases in this group. The outcome is good in these patients, and there is a role for partial nephrectomy for small tumors.[67] In a more recent multicenter prospective study, the incidence of tumor formation (including adrenal, liver, and visceral) in isolated hemihypertrophy was 5.9%.[68]

Children with Denys-Drash syndrome also have a high risk of Wilms' tumor formation, especially bilateral. It is recommended to perform bilateral nephrectomy of native kidneys before renal transplantation for end-stage renal disease.[69]

The risk of Wilms' tumor in sporadic aniridia was 6.3% in a population-based Danish study.[70] The salient features of children with WAGR syndrome were low birth weight and short stature at time of diagnosis. The outcome does not differ compared with children with WAGR syndrome except that late mortality secondary to end-stage renal disease is more common among the survivors.[71]

OTHER CHILDHOOD RENAL TUMORS

Congenital Mesoblastic Nephroma

Congenital mesoblastic nephroma is a tumor of infancy manifesting with asymptomatic palpable abdominal mass. Occasionally, infants may present with hematuria or hypercalcemia.[72] On CT scan, the tumor is cystic and often difficult to differentiate from cystic Wilms' tumor. More recently, a vascular ring sign (anechoic ring sign around the tumor) on ultrasound has been described; this is due to the vascularity (Fig. 50-13).[73] Histologically, the tumor may be classic, cellular, or mixed pattern. The tumor tends to infiltrate the surrounding tissue because of lack of a pseudocapsule. Radical nephrectomy is the treatment of choice. There is a tendency for relapse especially with the cellular type in about 10% cases. These relapses usually occur within the first year of life.[25] Chemotherapy has been suggested for the cellular type and gross residual disease or incomplete resection.[74]

Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney was previously considered to be a variant of Wilms' tumor, but it is actually a distinct variety of the primary renal tumor and accounts for 5% of the total renal tumors in childhood. There have been no associations with genetics or syndromes. The salient features are that these tumors tend to metastasize to brain and bone, and are unicentric and unilateral. Histologically, there are three patterns: classic (evenly dispersed network of fine arborizing vessels accompanied by a variable stroma), hyalinizing, and epithelioid. Immunohistochemistry shows positivity for vimentin. The primary treatment is nephrectomy followed by the adjuvant therapy as described earlier. The survival for stage 1 was 98% with an overall survival of 64% in NWTS. The prognostic factors were treatment with doxorubicin, stage, age at diagnosis, and tumor necrosis.[75]

Rhabdoid Tumors of the Kidney

Rhabdoid tumor of the kidney is another distinctive renal neoplasm in infants, becoming uncommon after age 5 years and constituting about 2% of pediatric renal tumors. The characteristic of this tumor is presentation with hypercalcemia and synchronous or metachronous brain metastasis. Histologically, the distinctive features are large cells with large vesicular nuclei, prominent single nucleolus, and large oval intracytoplasmic hyaline inclusions. Immunohistochemistry shows positivity for vimentin. These tumors are aggressive and invasive. Renal and extrarenal rhabdoid tumors carry homozygous deletion or mutation of the *hSNF/INI1* gene located at 22q11.2.[76] The treatment is nephrectomy and adjuvant therapy as described earlier. The overall survival is poor because of presentation at an advanced stage. NWTS has reported about 50% survival for completely resected and node-negative patients.[77]

Renal Cell Carcinoma

Renal cell carcinoma accounts for about 2% to 6% of childhood renal tumors. In a more recent review, the age of presentation was 7.9 years.[78] Symptomatic presentation in the form of hematuria and abdominal mass is common. Radiologically, it may be difficult to differentiate renal cell carcinoma from Wilms' tumor. The common histologic variety is papillary cell carcinoma.[79] Treatment is radical nephrectomy, although partial nephrectomy has been reported.[78] The overall survival is more than 80% with a mean follow-up of 4.9 years.[78]

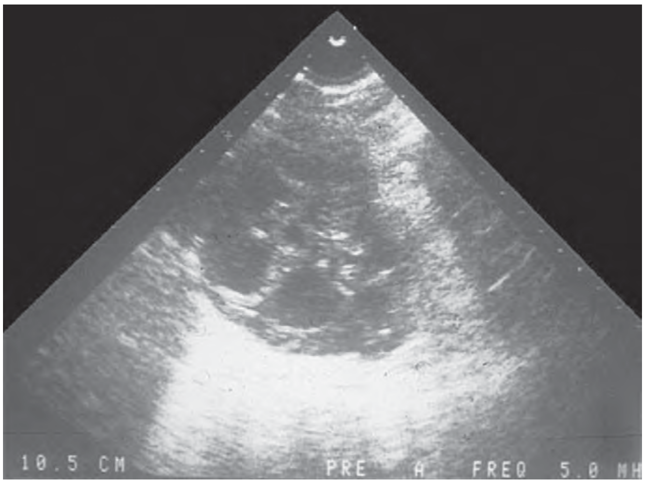


Figure 50-13 Ultrasound scan of mesoblastic nephroma.

PRENATAL RENAL TUMORS

Congenital mesoblastic nephroma is an infantile tumor, as discussed earlier. It can be diagnosed at 22 weeks of gestation with ultrasound, three-dimensional ultrasound, or MRI scan.[80] This tumor may be associated with polyhydramnios or hydrops fetalis. Occasionally, neonates may have hypertension.[81] Nephrectomy is performed when the neonate is stable.

There are few case reports of prenatal Wilms' tumor, which is a diagnostic dilemma. Prenatal biopsy has been suggested for confirmation of diagnosis and deciding the course of pregnancy.[82] In a complicated pregnancy, an emergency cesarean section has been suggested.[83] Prenatal Wilms' tumor needs further work and guidelines for management in view of its rarity.

According to the SIOP protocol, infants younger than 6 months with renal tumor should undergo primary nephrectomy after preoperative imaging and postoperative chemotherapy for appropriate tumor stage and histology. There is an option of close follow-up without chemotherapy in selected cases.[84]

ADULT WILMS' TUMOR

Wilms' tumor in adults has been reported by SIOP 93-01 with a median age at presentation of 25.4 years. These tumors tend to manifest at a more advanced stage and with the intermediate histology variety being the most common. The diagnosis and treatment are similar to the pediatric protocol. The event-free survival was reported as 57%, with an overall survival of 83% (median observation time 4 years).[85]

LATE EFFECTS OF THERAPY (CHEMOTHERAPY AND RADIOTHERAPY)

The long-term survival has improved because of the advances in the treatment of Wilms' tumor. Consequently, treatment-related factors have been shown to have an impact on various organs, subsequent health status, and quality of life in surviving children. Late effects of therapy were seen in more than two thirds of children treated for Wilms' tumor who had a combination of chemotherapy and radiotherapy.[86]

Second Malignant Neoplasm

SIOP has reported that the cumulative incidence of a second cancer observed at 15 years after Wilms' tumor diagnosis was 0.65%. This incidence was lower compared with previous SIOP trials and probably related to longer follow-up or might reflect changes in the treatment protocols.[87]

NWTS has reported that the cumulative incidence of a second malignant neoplasm was 1.6% and increased steadily with duration of follow-up. The risk factor was radiotherapy and the addition of doxorubicin to the treatment regimen.[88] In a more recent review, there was a 5.4% incidence of a second malignant neoplasm after radiotherapy for solid tumors, including Wilms' tumor. The median interval was 10.1 years (median radiation dosage was 45 Gy) from the diagnosis of initial primary tumor.[89] The incidence of acute myelogenous leukemia is also high according to NWTS. Of 5278 patients treated during the study period, 43 had second malignant neoplasms, and 7 of these 43 had acute myelogenous leukemia.[90] The other second neoplasms were chronic myelogenous leukemia and osteosarcoma.

Cardiac Dysfunction

Doxorubicin is known for its cardiotoxicity. SIOP has shown that post-treatment left ventricular fractional shortening was reduced in 2.5% of patients. Abnormal electrocardiogram findings that were not detectable before therapy were found in 5.6% of children. The median interval was 2.9 years from the median post-treatment interval.[91] This was very low, presumably secondary to the short post-treatment interval. In a large single institutional study, 25% of the anthracycline-treated group showed cardiac abnormalities. All but one of these patients had increased left ventricular afterload. The median interval for follow-up was 7.1 years. There was direct correlation with the dose and intensity.[92]

Pulmonary Dysfunction

The survivors of Wilms' tumor who have received the either whole-lung irradiation or abdominal radiation have abnormal pulmonary function in the form of reduced vital and total lung capacity.[93] Chemotherapeutic agents actinomycin D and doxorubicin potentiate the pulmonary dysfunction. Interstitial pneumonitis is also reported in the long-term follow-up.

Musculoskeletal System

Another consequence of radiotherapy with the addition of chemotherapy is abnormal musculoskeletal development. In a long-term review (median follow-up 15 years), the percentages of patients who developed muscular hypoplasia, limb-length inequality, kyphosis, and iliac wing hypoplasia were 16.7%, 11.9%, 7.1%, and 7.1%. Scoliosis was seen in 42.9% and was directly related to the duration of follow-up and radiation dose.[86] The surviving children have stature loss, which is radiation dose–dependent and age-dependent.[94] Osteopenia and imbalance of bone turnover, independent of radiotherapy, is seen in 27% of surviving children.[95]

Reproductive System

The germ cells are more sensitive to radiation damage than Leydig cells. In a long-term follow-up, survivors have shown impaired spermatogenesis.[96] Vincristine is also implicated as a risk factor for spermatogenesis. Ovarian failure after abdominal radiation was about 68%,[97] and there have been one or two small or absent ovaries and a small uterus[98] during the follow-up. Fertility can be preserved if the pelvis is excluded from the radiation field; NWTS has reported pregnancy in these patients.[99] Women who received flank radiation therapy as girls as part of their treatment for Wilms' tumors are at increased risk of fetal malposition and premature labor. The offspring of these women are at risk for low birth weight, premature (<36 weeks' gestation) birth, and occurrence of congenital malformations.[100]

Liver Dysfunction

Acute and chronic hepatitis is a sequela of radiation therapy. Concurrent administration of actinomycin D and vincristine causes severe toxicity and is dose-dependent.[101]

Renal Dysfunction

Chemotherapy or radiation field covering the remaining kidney or hyperfiltration leads to temporary or chronic nephropathy. A single institutional study showed renal dysfunction in 32%, including 19% with a low glomerular filtration rate (<80 mL/min/1.73 m^2), 11% with hypertension, and 9% with increased urinary albumin excretion, over a 13-year follow-up after treatment.[102] In contrast, in another study with a median follow-up of 8.8 years, there was an encouraging report that the treatment for Wilms' tumor rarely causes long-term renal impairment.[103] This change may be due to modified new protocols of treatment over last 15 years.

Behavioral and Educational Limitations

Children with Wilms' tumor, requiring various long-term therapies and frequent hospitalizations, can be presumed to have some behavioral and educational difficulties. This has not been seen in these children, however, compared with children with acute lymphoblastic leukemia from a multicenter study.[104]

FUTURE CHALLENGES

Work of NWTS and SIOP in relation to optimizing the management protocols for children with Wilms' tumor and finding the biologic parameters is ongoing and is expected to add to improved survival and reduction of long-term therapy-related toxicity. Immunotherapy[105] is a potential challenge for the future, with the hope that the current research will transpire into future therapy, especially the characteristic expression of *WT1* gene peptides and recognition by cellular and humoral immune responses, which acts as a potential target antigen in immunotherapeutic trials.

REFERENCES

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CHAPTER 51

RHABDOMYOSARCOMA

Berk Burgu and Duncan T. Wilcox

Rhabdomyosarcoma is the most common soft tissue sarcoma in infants and children; it is a malignancy that originates from primitive embryonal mesenchyme, which can, but does not necessarily, develop into striated muscle. It was first described in 1854 by Wiener, who reported a case of rhabdomyosarcoma in an adult with a tumor on the tongue.[1] It was not until the 1950s that a series of children with rhabdomyosarcoma was reported.[2] In the same decade, the two histologic subtypes, embryonal and alveolar, were characterized, and this led Horn and Enterline[3] to outline their histologic classification, which is still widely used today.

Surgical excision remained the mainstay of therapy until the 1950s, when Stobbe and Daregeon[4] showed that outcomes could be improved with the addition of radiotherapy. This method was later modified by the introduction of high-dose radiotherapy in the 1960s. In the late 1950s and early 1960s, various chemotherapeutic agents were found to be beneficial, including vincristine, actinomycin D, and cyclophosphamide. In 1959, D'Angio recognized that actinomycin D and radiotherapy combined had a synergistic effect on outcomes.[1] By 1961, Pinkel and Pinkren[5] advocated complete surgical excision followed by chemotherapy and radiotherapy. They acted as the catalyst for modern-day multimodal therapy and the introduction of large multicenter trials on the treatment of rhabdomyosarcoma.

Cure rates have improved substantially in the last 3 decades; there has been a steady increase in the 5-year survival from approximately 30% to 75% today. In addition, with modern multidisciplinary therapy, there has been a reduction in treatment-related morbidity. This improvement has been the direct result of a series of large multicenter trials. These have been organized by the Intergroup Rhabdomyosarcoma Study (IRS) group and the International Society of Pediatric Oncology (SIOP). These trials have studied and refined the use of multimodal therapy, including chemotherapy, radiotherapy, and surgery, with great success.

Rhabdomyosarcoma is the cause of 4% to 8% of all malignant disease occurring in children younger than 15 years and is one of the five most common malignant tumors of childhood (Fig. 51-1).[6] Approximately 350 new cases occur each year in the United States.[7] In the United States, the incidence is greater in whites than in African-Americans (4:3 ratio), and boys seem to be more commonly affected than girls (3:2 ratio). The incidence of rhabdomyosarcoma has two distinct peaks. The first peak, encompassing more than 50% of cases, occurs in the first decade of life and is primarily embryonal or botryoid. This type tends to occur in the body cavities, the head and neck region, or the genitourinary tract with most patients alive 5 years after therapy. The second peak occurs during adolescence and consists largely of alveolar type, which are often seen in the extremities and metastasize early in the course of disease; these patients have a poorer prognosis.[8] Most genitourinary tumors, excluding paratesticular rhabdomyosarcoma, occur in children younger than 4 years.[9]

Rhabdomyosarcoma can develop in any part of the body that contains embryonal mesenchyme; although this implies tumor derived from striated muscle, typically it arises in tissue lacking striated muscle. The common sites for rhabdomyosarcoma are presented in Figure 51-2. In this chapter, only tumors arising in the genitourinary tract are discussed further.

ETIOLOGY

The cause of rhabdomyosarcoma is unknown, but is thought to be multifactorial. Most tumors occur sporadically, with no predisposing risk factors. Congenital and environmental factors have been shown to influence the incidence of rhabdomyosarcoma, however. In a large epidemiologic study, 5% of affected children were found to have a strong family history.

Congenital Rhabdomyosarcoma

Rhabdomyosarcoma is associated with Li-Fraumeni syndrome, neurofibromatosis, Noonan syndrome, Beckwith-Wiedemann syndrome,[10] Costello syndrome,[11] fetal alcohol syndrome, and basal cell nevus syndrome (Table 51-1). Li-Fraumeni syndrome has an autosomal dominant inheritance.[12-14] The diagnosis of Li-Fraumeni syndrome raises the problem of preventive screening for mutation carriers who have a high lifetime risk of malignancy—estimated 73% for male carriers and 100% for female carriers.[15] These families have various malignant conditions, including rhabdomyosarcoma, breast cancer, brain tumors, adrenal carcinoma, and leukemia. Typically, families have a history of premenopausal breast cancer, and the child is usually male and younger than 2 years.[12] A diagnosis of Li-Fraumeni syndrome should be considered in every child younger than 3 years diagnosed with rhabdomyosarcoma.[15] This syndrome has been linked with abnormalities of the tumor-suppressor gene *p53*, which is located on the short arm of chromosome 17.[16] The gene *p53* controls cellular DNA damage during cell proliferation; a defect in this function can lead to abnormal cell proliferation. Independent of Li-Fraumeni syndrome, mutations of the *p53* gene have been identified in 10% of children with rhabdomyosarcoma.[17]

Patients with neurofibromatosis 1 are at greater risk of several malignancies. A study from IRS IV reported the prevalence of neurofibromatosis 1 in children diagnosed with rhabdomyosarcoma as approximately 0.5%. Rhabdomyosarcoma of bladder and prostate were more common in this group of patients and did not seem to be different from other children with rhabdomyosarcoma in terms of prognosis.[18] Patients who develop a second malignancy after successful treatment of rhabdomyosarcoma may have a genetic predisposition, with Li-Fraumeni syndrome, neurofibromatosis, and chromosomal translocations occurring with a greater than expected incidence in these patients.[1]

Costello syndrome is a rare congenital anomaly syndrome associated with an increase in the number of solid tumors, the most common being rhabdomyosarcoma followed by neuroblastoma and bladder carcinoma. The tumor frequency in these patients is 17%. It may be classified as an overgrowth syndrome because of slightly increased birth weight and relative macrocephaly; it is characterized by severe postnatal failure to thrive and short stature.[11] With a better understanding of the human

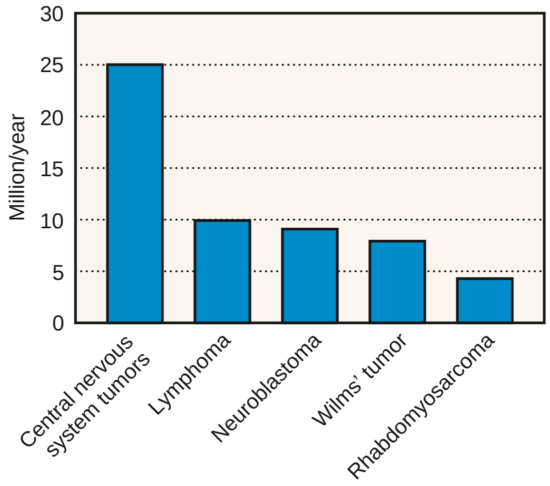

Figure 51-1 Most common malignant tumors of childhood.

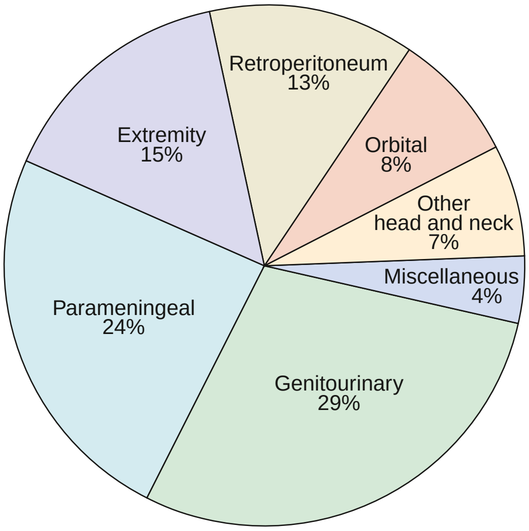

Figure 51-2 Presenting sites for rhabdomyosarcoma.

genome, chromosomal and gene anomalies are increasingly being identified in patients and families with rhabdomyosarcoma. This topic is discussed more extensively in Chapter 49.

Acquired Rhabdomyosarcoma

Many environmental factors have been implicated in rhabdomyosarcoma; these may work in conjunction with or independently of genetic risk factors. Chemical risk factors include chlorinated phenoxy herbicides, parental use of marijuana, parental use of cocaine, and maternal alcohol ingestion.[19] Maternal exposure to radiation and a maternal history of stillbirths also increase the tumor risk to the fetus.[20] Some animal studies have suggested a link with viral illness, although this has not been identified in humans.

PATHOLOGY

Anatomic Sites

Pediatric urologists see patients presenting with rhabdomyosarcoma arising from the urinary tract, genital tract, and other nongenitourinary sites in the pelvis. The most common sites are the prostate, bladder (which mainly affects the trigone region), vagina, and paratesticular region. Other sites include the uterus, cervix, and ureter. Paratesticular rhabdomyosarcoma is discussed further in Chapter 52.[9]

Table 51-1 Risk Factors for Rhabdomyosarcoma

Congenital
Li-Fraumeni syndrome
Neurofibromatosis
Basal cell nevus syndrome
Fetal alcohol syndrome
p53 mutations
Noonan syndrome
Beckwith-Wiedemann syndrome
Costello syndrome
Acquired
Marijuana
Cocaine
Maternal exposure to radiation
Maternal history of stillbirths

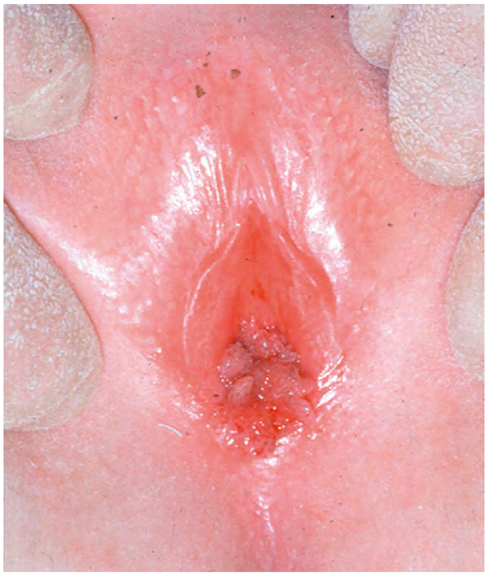

Figure 51-3 Sarcoma botryoides. Notice the tumor prolapsing from the vaginal orifice.

Macroscopic Appearance

There are no specific gross features of rhabdomyosarcoma except sarcoma botryoides. This is a tumor that arises from a hollow organ, typically the vagina or bladder, and usually manifests as a prolapsing tumor resembling a bunch of grapes (Fig. 51-3). Children younger than 4 years typically present with sarcoma botryoides. The remaining tumors are normally firm and nodular; they appear to be well circumscribed when they actually are often infiltrating surrounding tissues.

Table 51-2 Histologic Classification of Rhabdomyosarcoma

Diagnosis	Histology	Incidence(%)*	5-Year Survival (%)	Prognosis
Embryonal, botryoid	Favorable	6	95	Good
Embryonal, spindle cell	Favorable	3	88	Good
Embryonal, NOS	Favorable	49	66	Intermediate
Alveolar, NOS or solid variant	Unfavorable	31	53	Poor
Anaplasia, diffuse	Unfavorable	2	45	Poor
Undifferentiated sarcoma	Unfavorable	3	44	Poor

*Total incidence is only 94%; approximately 6% of accepted cases fall into the sarcoma NOS category because of insufficient or inadequate tissue to make a more specific diagnosis.

NOS, not otherwise specified.

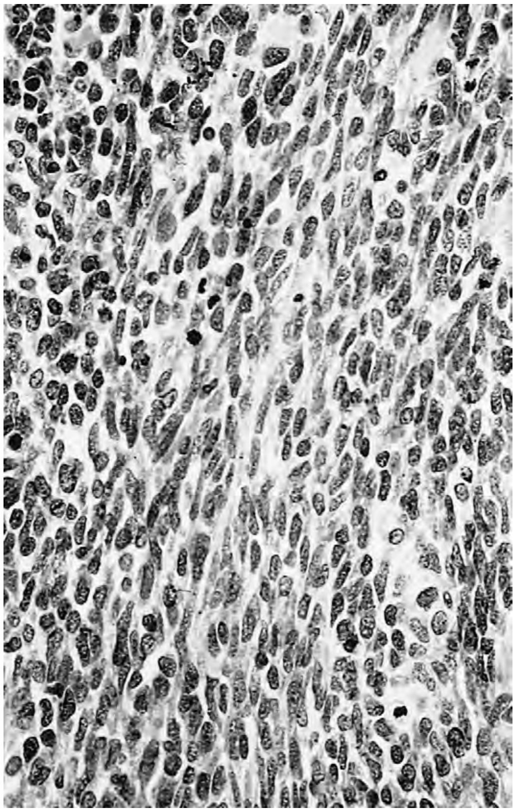

Figure 51-4 Histologic slide shows embryonal rhabdomyosarcoma. (Courtesy of the Department of Histopathology, Great Ormond Street Hospital for Children NHS Trust, London, UK.)

Microscopic Appearance and Classification

The IRS definition of rhabdomyosarcoma is "sarcoma showing exclusive evidence of skeletal muscle differentiation by morphologic or ancillary techniques."[8] The differing morphologic features of rhabdomyosarcoma were recognized in the mid-1900s by Horn and Enterline[3] with their division of rhabdomyosarcomas into embryonal, alveolar, botryoid, and pleomorphic subtypes. More recent histologic and biologic studies have resulted in description of additional entities and refinements in recognition of the original entities, such as solid-alveolar rhabdomyosarcoma. Classification based solely on histology is not easy, however, and does not always allow unambiguous subclassification. The international classification of rhabdomyosarcoma was defined based on the original Horn and Enterline classification because of a need to develop a single significant classification of rhabdomyosarcomas that is also prognostically meaningful. Table 51-2 shows the international classification of rhabdomyosarcoma.[8] For practical purposes, the histology can be divided into two main subgroups: the favorable group, comprising embryonal rhabdomyosarcoma and its variants, and the unfavorable group, comprising alveolar rhabdomyosarcoma, anaplastic variant, and undifferentiated sarcoma.

Rhabdomyosarcoma must be distinguished from neuroblastoma, Ewing sarcoma, and lymphoma. The correct identification of rhabdomyosarcoma is a challenge. Using a central review mechanism for patients enrolled in IRS studies, 20% of children enrolled are found to be incorrectly diagnosed or have their histologic subtype reclassified. An adequate biopsy specimen is crucial for special histochemical stains and molecular studies; fine-needle biopsies are generally inappropriate. Malignant skeletal muscle differentiation distinguishes rhabdomyosarcoma from other round blue cell neoplasms.[7]

Embryonal Rhabdomyosarcoma

Embryonal rhabdomyosarcoma is the most common type, occurring in approximately 80% of genitourinary tumors. These tumors tend to occur in younger children and at more favorable sites.[7] The tumor resembles fetal striated muscle at 7 to 10 weeks of gestational age. The cells are spindle-shaped or spindle-shaped and round in a loose myxoid or collagenous matrix. The cells tend to have round or oval nuclei with eosinophilic cytoplasm. Cross-striations occur in about 30% (Fig. 51-4).[21] Sarcoma botryoides is a variant of the embryonal type. It is a polypoid mass composed of small round cells in loose stroma. Classically, there is a dense tumor cell layer under the epithelium (cambium layer).[22] The botryoid variant is associated with the best prognosis. An extensive degree of rhabdomyoblastic differentiation can be evident in the cambium layer and elsewhere in the neoplasm. The embryonal spindle cell variant also has a good prognosis, but is found only in paratesticular tumors and rarely in some head and neck lesions.[21] The neoplasm has a fascicular spindled "leiomyomatous" growth pattern, which can show a marked degree of differentiation; some tumors show marked collagen deposition and assume a more nested pattern.

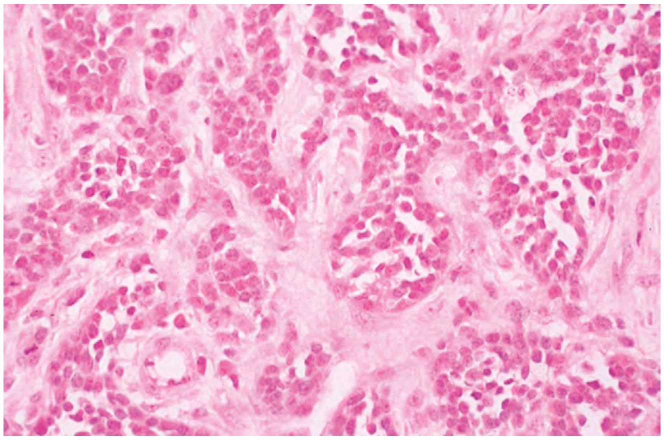

Figure 51-5 Histologic slide shows alveolar rhabdomyosarcoma. (Courtesy of the Department of Histopathology, Great Ormond Street Hospital for Children NHS Trust, London, UK.)

Alveolar Rhabdomyosarcoma

Alveolar rhabdomyosarcoma is the next most common type; it usually occurs in older children and in adults. It resembles 10- to 21-week gestational striated muscle. The features are clusters of small round cells adherent to fibrous septa, giving the appearance of well-defined alveolar spaces. Cross-striations are uncommon (Fig. 51-5). Occasionally, there are clusters of cells separated by fibrous septa, but the alveolar spaces are not present. These are called solid alveolar rhabdomyosarcoma.[21] There is no evidence of a different prognosis for solid versus classic alveolar rhabdomyosarcoma, but both have a poor prognosis.[8] Some tumors can have features of embryonal and alveolar types and are classified as mixed tumors.

Anaplastic (Pleomorphic) Rhabdomyosarcoma

The category of pleomorphic rhabdomyosarcoma as originally defined by Horn and Enterline corresponds to the anaplastic group. They are characterized by various cell types from large cells with multiple nuclei to spindle-shaped cells. Anaplastic rhabdomyosarcoma was defined by large, lobate hyperchromatic nuclei and atypical mitotic figures. This pattern can be focal or diffuse. The occurrence of anaplasia is independent of either tumor site or subtype, although it occurs preferentially in embryonal rhabdomyosarcoma. It has proven to be a poor prognostic determinant.

Undifferentiated Rhabdomyosarcoma

Some tumors are so undifferentiated that it is difficult to classify them. They are composed of primitive, small round cells that can often resemble Ewing sarcoma. The difference is that they arise from soft tissue not bone. With an increasing understanding of the immunohistochemistry of these tumors, undifferentiated tumors now can frequently be identified as rhabdomyosarcomas. Rhabdomyosarcoma tumors frequently express the muscle proteins actin, myosin, and desmin.[23,24] In addition, with electron microscopy, the Z bands associated with actin-myosin bundles can help to distinguish rhabdomyosarcoma from other small round cell tumors. Perhaps the most sensitive and specific group of proteins useful in the immunohistochemical diagnosis of rhabdomyosarcoma are muscle transcription factors MyoD and myogenin. These proteins, which define the earliest events in molecular determination of myoblastic lineage, are paradoxically expressed at high levels in most rhabdomyosarcomas, even though the cells often show little differentiation.[25] Clinically, this scaled-down category occurs more often in boys 5 years old or older.[8]

Molecular Biology and Genetic Features

With a better understanding of the human genome, chromosomal and gene anomalies are increasingly being identified in patients and families with rhabdomyosarcoma. Embryonal and alveolar tumors can now be identified by different structural chromosomal changes. Embryonal tumors have a loss of heterozygosity on the long arm of chromosome 11. The paternal DNA appears duplicated, with the maternal DNA absent. Although a single key genetic mutation cannot be identified in embryonal rhabdomyosarcomas, aberrations affecting the methylation status of key genes such as *MyoD*[26] and *p21*[27] have been identified. These findings suggest embryonal rhabdomyosarcoma may be epigenetic rather than genetic.

In alveolar rhabdomyosarcoma, key genetic mutations have been identified. Unique gene fusions of *PAX3* or *PAX7* (on chromosomes 1 and 2) and the FOXO1a (*FKHR*) gene on chromosome 13 specifically identify alveolar rhabdomyosarcoma.[28] Most alveolar tumors express PAX3-FKHR or PAX7-FKHR gene fusions resulting from t(2;13) or t(1;13) translocations. The *PAX-3* gene, which is involved in transcription regulation, is moved to a site close to *FKHR*, which is part of the forkhead family of transcription factors. Of the alveolar rhabdomyosarcoma patients involved in IRS IV, 55% had PAX3-FKHR and 22% had PAX7-FKHR fusion transcripts. All other patients lacked these transcripts. In patients presenting with metastatic disease, the survival rate was significantly higher in patients with PAX7-FKHR fusion transcripts (75%) compared with patients who had PAX3-FKHR fusion (8%). These patients have a significantly increased risk of failure and death.[29,30] Both translocations can now be identified by polymerase chain reaction and can be used to diagnose alveolar rhabdomyosarcoma and may predict outcome.

Increased transcriptional levels of some growth factors or receptors in rhabdomyosarcomas are found to be associated with survival. Rhabdomyosarcomas with increased platelet-derived growth factor receptors and insulin-like growth factor (IGF) were associated with decreased survival.[31] The loss of heterozygosity in embryonal rhabdomyosarcomas is closely approximated with the IGF-II gene, which can lead to overexpression of IGF-II.[32] Alveolar and embryonal tumors produce excess IGF-II, and in experimental studies, blocking IGF receptors resulted in an inhibition of tumor growth.[33,34]

Tumor Spread

Rhabdomyosarcoma can spread by local infiltration into surrounding tissues. This depends on the site of the primary tumor, but it is unusual for tumors to spread into the rectum. Pelvic tumors also can spread directly to the omentum. Spread to local and regional lymph nodes is also a common feature, occurring in approximately 20% at presentation.[35] Distant metastatic spread is present in nearly a quarter of patients, and the most frequently affected sites are the lung (40% to 50%), bone marrow (20%), and bone (10%); metastases to liver and brain are rare.[22,36,37]

CLINICAL FEATURES

The presenting signs and symptoms of rhabdomyosarcoma vary and depend on the site of the local disease and the presence or absence of metastatic spread.

Table 51-3 Presenting Clinical Features of Rhabdomyosarcoma

Cause of Presenting Feature	Symptoms and Signs
Visible tumor	Abdominal mass
	Prolapsing tumor (sarcoma botryoides)
Bladder outlet obstruction	Strangury
Mucosal damage	Urinary infection
	Urinary retention
	Urinary incontinence
	Hematuria
	Vaginal discharge
	Passing tumor fragments

Local Disease

The most common presenting feature of the primary tumor site is the visible sign of the tumor. This can occur in two ways—either as a prolapsing mass seen with sarcoma botryoides or as a large abdominal mass (Table 51-3). These tumors often manifest as an abdominal mass because pelvic tumors can grow very large before they impinge on the surrounding rectum or bladder sufficiently to cause symptoms. Other presenting features are signs of bladder outlet obstruction or mucosal damage or both.[38,39]

Distant Spread

Approximately 25% of patients have metastatic spread at the time of presentation.[37] A few patients present only with systemic signs associated with diffuse metastatic spread; these include fever, weight loss, anorexia, and pain. In these patients, the site of the primary tumor may become apparent only after considerable investigation.

INVESTIGATIONS

Blood and Urine

Hematologic investigations should include hemoglobin level, a white blood cell analysis, a platelet count, and clotting studies. Serum chemistry studies to evaluate renal and liver function are required. In contrast to the situation with neuroblastoma and liver tumors, no specific serum or urine markers of rhabdomyosarcoma have been identified. In some patients, creatine kinase levels are increased, which can give a clue to the underlying diagnosis. Standard urinalysis is necessary to exclude concurrent urinary tract infections.[22]

Imaging

Accurate reproducible imaging is vital to the successful management of children with rhabdomyosarcoma. Imaging is required to identify the organ of origin and to assess the surgical management options. It is also used to identify local and metastatic spread. In addition, after therapy is initiated, imaging is used to monitor tumor responses.[40]

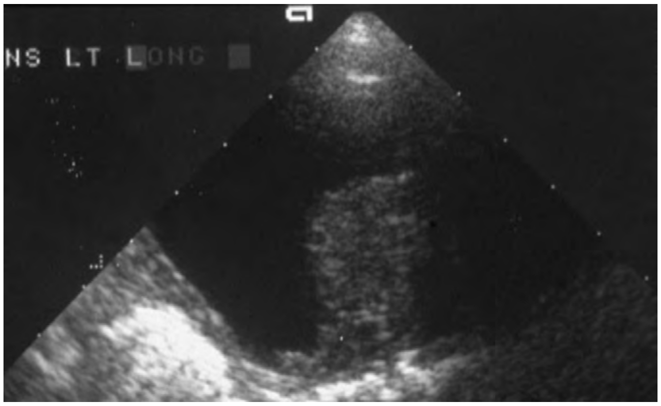

Figure 51-6 Ultrasound scan shows a transverse section through the bladder. The rhabdomyosarcoma can be seen clearly within the bladder.

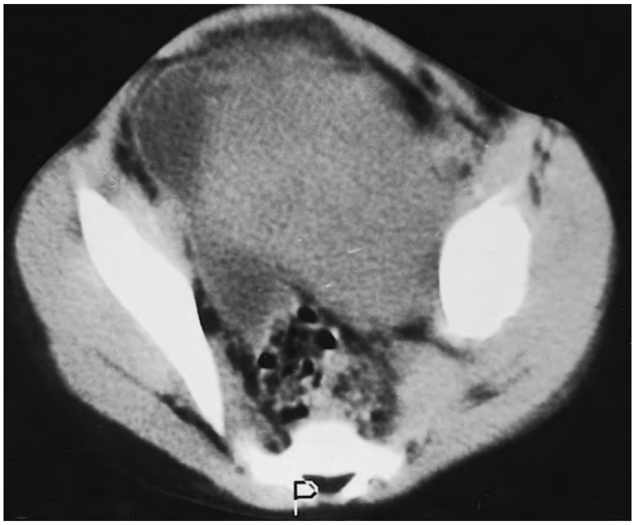

Figure 51-7 CT scan shows pelvic rhabdomyosarcoma arising from the bladder.

Local Disease

The initial imaging is often performed using ultrasound (Fig. 51-6); however, once a tumor has been confirmed, cross-sectional imaging of the primary site is required. Either computed tomography (CT) (Fig. 51-7) or magnetic resonance imaging (MRI) can be used. Both should be performed using intravenous contrast material, with care being taken to record measurements of the tumor in at least two directions.[40] In terms of diagnostic accuracy, there is little difference between CT and MRI, although CT may be superior in assessing abdominal lymphadenopathy. Because of the lack of ionizing radiation and multiplanar capabilities, MRI is recommended by many radiologists.[40] To ensure consistent imaging, the same modality should be used to follow the tumor response to therapy. In addition to visualization of the primary tumor site, the local and the regional lymph nodes must be identified.

Although MRI is recommended for all genitourinary tumors, it has its problems. Edema after radiotherapy can be misinterpreted as residual disease in 20% of cases, using cross-sectional imaging techniques.[41] On T2-weighted images, urine images brightly, and this can obscure tumor in the bladder wall. Gadolinium enhancement is probably best avoided because it can lead to layered contrast material in the bladder, which can confuse interpretation.

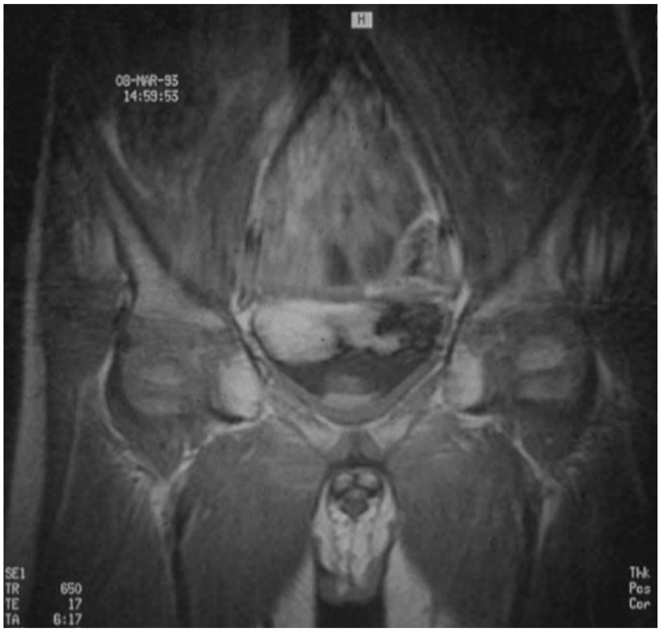

Figure 51-8 MRI shows a pelvic rhabdomyosarcoma arising from the bladder. Only a small rim of the bladder lumen is still visible.

Despite this, T1-weighted and T2-weighted images in coronal and sagittal planes provide the best imaging on which to base clinical decisions (Fig. 51-8). Historically, contrast cystograms and intravenous urograms were used to outline bladder lesions; however, extravesical spread of the lesion was difficult to assess. With advances in cross-sectional imaging, these are rarely necessary today (Fig. 51-9).

Distant Spread

At the initial presentation, distant metastases are present in 25% of patients; consequently, the common sites for distant metastases require imaging. Chest CT should be used to identify lung metastases even in the presence of a normal chest radiograph. Where available, spiral CT should be used in preference to conventional CT because it is superior in detecting lung lesions.[40] Positron emission tomography has been used to detect metastases, but it is not considered a standard staging tool for rhabdomyosarcoma currently.[7]

Bone marrow aspiration is used to investigate marrow invasion, and bone scintigraphy can record the presence of skeletal metastases. Bone scintigraphy, similar to all investigations, has false-negatives and identifies lesions in only 4% of patients.[40] This situation has caused some investigators to recommend bone scans only for patients with bone symptoms or patients whose tumor has an unfavorable histologic appearance. This approach is still controversial.

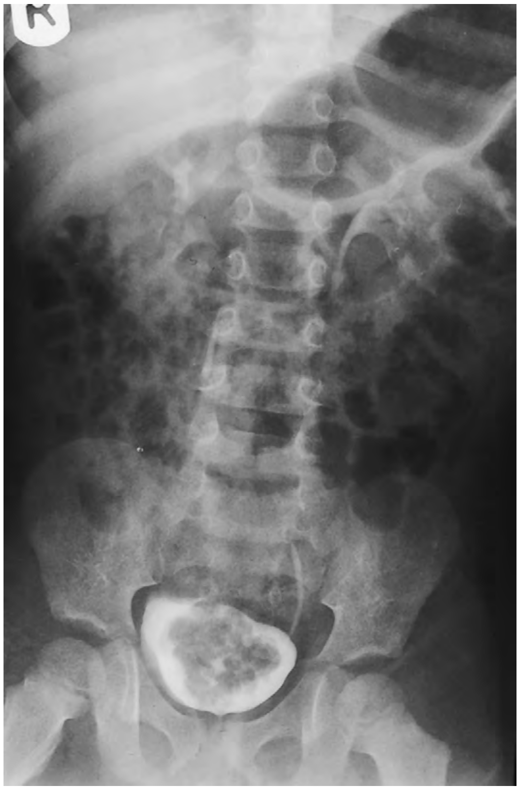

Figure 51-9 Intravenous urogram shows bladder rhabdomyosarcoma as a filling defect within the bladder.

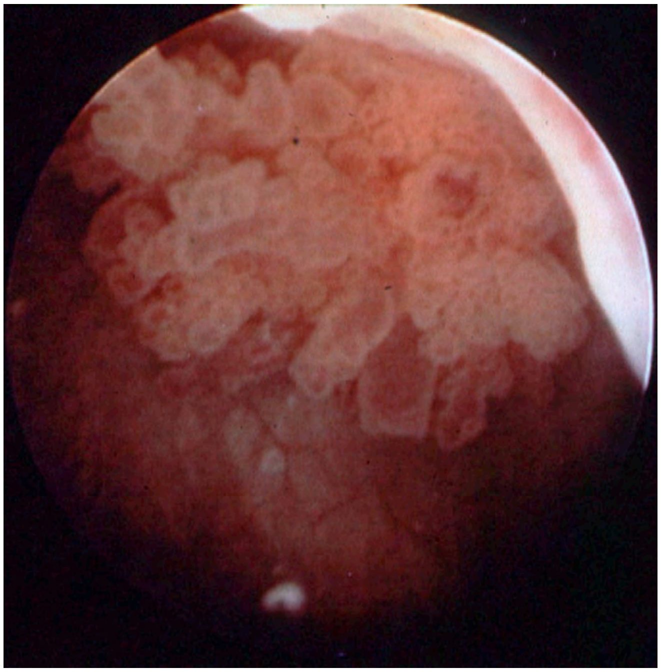

Figure 51-10 Endoscopic view of a bladder papilloma.

Endoscopy

Patients in whom tumor in the bladder or vagina and uterus is suspected on clinical and radiologic investigations require endoscopy (Fig. 51-10). Endoscopy can be used to delineate further the extent of the tumor and obtain tissue biopsy specimens. The advantages of endoscopic biopsy are that the risk of needle tract seeding is eliminated, and it is less invasive than open biopsy. Technically, obtaining a satisfactory biopsy specimen for tissue diagnosis can be difficult. Care must be taken to avoid destroying the histologic appearance of the tissue by the overuse of the diathermy. Where possible, the biopsy specimen should be taken as close to the bladder or vaginal wall as possible; this should ensure sufficient tissue for diagnosis. In rare patients, accurate tissue diagnosis cannot be made using endoscopic biopsy, and an open or percutaneous method is necessary.

Table 51-4 Differential Diagnosis of Pelvic Rhabdomyosarcoma

Neurofibroma
Lymphohemangioma
Leiomyosarcoma
Transitional cell carcinoma
Adenocarcinoma
Clear cell adenocarcinoma
Benign adenosis
Squamous cell carcinoma
Inflammatory pseudotumor

From Snyder H, D'Angio G, Evans A, Raney R. Pediatric oncology. In: Walsh P, Retik A, Vaughan E, Wein A, eds. *Campbell's Urology*. 7th ed. Philadelphia: Saunders; 1998:2210-2256.

Differential Diagnosis

Although rare, numerous tumors can mimic pelvic rhabdomyosarcoma (Table 51-4). In patients who present with a prolapsing tumor indicating sarcoma botryoides, vaginal prolapse, urethral prolapse, prolapsing ureterocele, and rare urethral polyps should be excluded.

Clinical Staging

The two main study groups, IRS and SIOP, have staged rhabdomyosarcoma using two different systems. SIOP uses a pretreatment TNM staging system.[42-44] Since its inception, IRS has devised and has continued to use a staging system that classifies these tumors by IRS group, which is determined by extent of the initial tumor resection (Table 51-5). One of the difficulties inherent in this system is that the staging depends on the surgical excision. This can lead to interpatient staging variability, depending on the extent of surgical resection individual surgeons perform.

Since the early 1990s, IRS has also used a clinical staging system, which is a modification of the TNM staging system that is based on the pretreatment assessment of tumor site and size and regional and systemic tumor spread (Table 51-6).[45] This system depends on the tumor invasiveness (T1 means the tumor is confined to the anatomic site; T2 means extension of tumor); the tumor size (<5 cm [Ta] or >5 cm [Tb]); the clinical presence (N1) or absence of nodes (N0); and the presence (M1) or absence (M0) of distant metastases. This system has been modified to take into account the different outcomes associated with sites.[22] The disadvantage of the TNM system is that it can be difficult to identify tumor-positive nodes accurately on imaging, or to differentiate them from inflammatory nodes. This difficulty can lead to errors in pretreatment staging; however, with improvements in imaging techniques, the incidence of staging errors should be reduced.

Table 51-5 Intergroup Rhabdomyosarcoma Study Clinical Grouping Classification

Group I—Localized Disease, Completely Resected

Regional nodes not involved

A—Confined to organ of origin

B—Contiguous involvement—infiltration outside the organ of origin

Notation: This includes gross inspection and microscopic confirmation of complete resection. Any nodes that may be inadvertently taken with the specimen must be negative. If the latter should be involved microscopically, the patient is placed in group IIB or group IIC (see below).

Group II—Total Gross Resection with Evidence of Regional Spread

A—Grossly resected tumor with microscopic residual disease. Surgeon believes that all the tumor has been removed, but pathologist finds tumor at the margin of resection, and additional resection to achieve a clean margin is not feasible. No evidence of gross residual tumor; no evidence of regional node involvement; when radiotherapy or chemotherapy or both have been started, re-exploration and removal of the area of microscopic residual does not change the patient's group.

B—Regional disease with involved nodes, completely resected with no microscopic residual

Notation: Complete resection with microscopic confirmation of no residual disease makes this different from group IIA and group IIC. Additionally, in contrast to group IIA, regional nodes (which are completely resected) are involved, but the most distal node is histologically negative.

C—Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual or histologic involvement or both of the most distal regional node (from the primary site) in the dissection

Notation: The presence of microscopic residual disease makes this group different from group IIB, and nodal involvement makes this group different from group IIA.

Group III—Incomplete Resection with Gross Residual Disease

A—After biopsy only

B—After gross or major resection of the primary (>50%)

Group IV—Distant Metastatic Disease Present at Onset

Lung, liver, bones, bone marrow, brain, and distant muscle and nodes

Notation: The above excludes regional nodes and adjacent organ infiltration, which places the patient in a more favorable grouping (as noted under group II). The presence of positive cytology in the cerebrospinal fluid or pleural or abdominal fluids, and implants on pleural or peritoneal surfaces are regarded as indications for placing the patient in group IV.

TREATMENT

Initial Treatment

Initial management is the symptomatic treatment of the presenting symptoms and a prompt diagnosis. If bladder drainage is required, urethral catheterization is preferred because suprapubic drainage has resulted in the seeding of malignant cells along the tract, leading to local recurrence. A tissue diagnosis is required before adjuvant therapy is begun. If possible, the tissue specimen should be obtained endoscopically to avoid tract seeding; if this is not possible, the approach to biopsy requires careful consideration. Ideally, the site of the Tru-Cut biopsy should be planned so that at excisional surgery the biopsy site can be incorporated in the surgical incision. Generally, an adequate biopsy specimen can be obtained using a Tru-Cut needle; rarely, a surgical biopsy is required.

Table 51-6 **Intergroup Rhabdomyosarcoma Study Modified TNM Pretreatment Staging Classification**

Stage	Sites*	T	Size†	N	M
1	Favorable	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Unfavorable	T1 or T2	a	N0 or Nx	M0
3	Unfavorable	T1 or T2	a	N1	M0
			b	N0 or N1 or Nx	M0
4	All	T1 or T2	a or b	N0 or N1	M1

*Favorable sites are the genitourinary system excluding bladder/prostate. Unfavorable sites are the bladder/prostate and retroperitoneum.

†Pretreatment size is determined by external measurement using MRI or CT, depending on the anatomic location. For less accessible primary sites, CT is used as a means of lymph node assessment as well. Metastatic sites require some form of imaging (but not histologic confirmation except for bone marrow examination) confirmation.

Curative Treatment

All patients with rhabdomyosarcoma are presumed to have micrometastatic disease at diagnosis. The current standard treatment includes a combination of chemotherapy with or without adjuvant radiotherapy and surgical excision as a specific treatment directed at control of primary site.[7]

Principles of Chemotherapy

Early clinical trials concentrated on examining the effect of single-agent chemotherapy. From these studies, many agents, such as actinomycin D, cyclophosphamide, vincristine, and doxorubicin, were found to be effective, although few patients were cured.[46] Use of these agents in combination led to an improvement in survival. In the early 1960s, Pinkel and Pinkren[5] described combining surgery and radiotherapy with prophylactic chemotherapy. When chemotherapy was added to the therapy, survival increased from 47% to 85%.[47] After these studies, Wilbur[48] expanded this use of chemotherapy and gave repeated doses of vincristine, actinomycin D, and cyclophosphamide to children with inoperable or metastatic disease. Using this approach, Wilbur was able to prolong survival in these patients.[48] These initial studies showed that combination chemotherapy can downstage inoperable tumors to operable, and can improve survival in children with rhabdomyosarcoma.

Since these pioneering studies, large collaborative study groups have been set up to identify new drug regimens, improve survival, and reduce therapy-induced morbidity. The current standard treatment for rhabdomyosarcoma established by IRS studies includes vincristine and actinomycin D (VA), and vincristine, actinomycin D, and cyclophosphamide (VAC). For the more favorable subset of low-risk patients, IRS studies showed a 95% overall survival rate by VA therapy. In metastatic rhabdomyosarcoma, using an upfront window design, IRS studies have established the activity of many agents in newly diagnosed patients, including ifosfamide-doxorubicin, ifosfamide-etoposide, melphalan-vincristine, topotecan (an inhibitor of the enzyme topoisomerase), topotecan-cyclophosphamide, and irinotecan. The overall survival in the high-risk metastatic group remained low.[7] In this group of patients, consolidation using a high-dose chemotherapy regimen with hematopoietic stem cell rescue has been tried, but had no impact on overall outcome.[49]

Particularly for higher risk newly diagnosed patients, new treatment strategies are needed. The identification of new treatment targets through gene expression analyses, such as *p53* and *met*, holds great promise for treatment of rhabdomyosarcoma.[50,51]

Principles of Radiotherapy

Since Stobbe and Daregeon[4] showed an improved outcome when radiotherapy was added to surgical treatment in the 1950s, radiotherapy has frequently been used to treat patients with rhabdomyosarcoma. Radiotherapy as adjunctive therapy is able to damage and destroy malignant cells that remain after surgery and malignant cells in areas that are technically challenging for surgical removal. IRS I addressed the question of radiotherapy and concluded that radiotherapy incurred no benefit for group 1 patients, who had completely removed local disease; the radiation dose needed to be adjusted according to the patient's age; and the radiation field needed to be 5 cm beyond the tumor.[22,47] IRS II and III studies have altered these recommendations slightly, and for IRS IV, the radiation dose is not altered for the histologic type, tumor size, or patient's age.[9,52] The radiation field for pelvic tumors has been reduced to 2 cm beyond the tumor margin.

Radiotherapy is now restricted to patients with residual or metastatic disease, and a dose of 40 to 60 Gy is normally used; in very young children, this dose may be reduced.[1] IRS IV reported the results of hyperfractionated radiotherapy given twice daily with at least 6 hours between doses, with no difference in the failure-free survival or overall survival between hyperfractionated and conventional application.[53] The role of a locally applied radiation source (brachytherapy) either postoperatively or at the time of surgery is now being explored or reported with satisfactory results in some series with small numbers of patients.[54] The theoretical advantage of hyperfractionated therapy and brachytherapy is that acute toxicity and late-effect complications are reduced.[22]

Principles of Surgery

For many years, complete primary surgical excision of the tumor was the only hope of survival. Long-term survival varied from 40% for vaginal tumors to 70% for bladder tumors.[42] Surgery often involved complete pelvic exenteration. This form of radical surgery, even when successful, resulted in enormous morbidity. With the advent of chemotherapy and radiotherapy, it has become possible to perform less aggressive, organ-preserving therapy without altering survival. The role of surgery is now restricted to initial biopsy and then reassessment after induction chemotherapy. If there is complete response to chemotherapy on imaging, there is no need for an operation and biopsy to confirm the absence of tumor. If there has been a partial response to therapy, surgery can achieve a complete remission in more than 50% of patients. Whenever possible, surgery should be restricted to wide local excision, with emphasis on preserving organ function. In the few patients with unresponsive primary disease and in patients with local recurrence, more radical organ-removing surgery is required. In patients who require secondary radical surgery, survival is still greater than 80%.

Current therapy relies on tissue biopsy followed by multiagent chemotherapy; after this, repeat imaging is performed. If there is complete remission, chemotherapy is continued alone. If there is partial remission, a second operation to excise the tumor is performed. Second-look surgery after therapy may

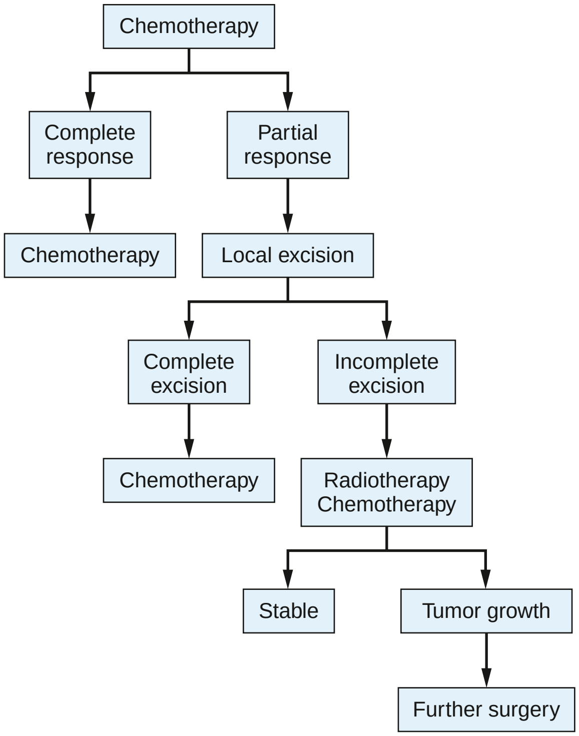

Figure 51-11 Algorithm for rhabdomyosarcoma treatment.

yield prognostic information about response to treatment. It is suggested that favorable outcome occurs when tumor cells have undergone maturation.[55] Cytodifferentiation or maturation of tumor cells to a phenotype that more resembles skeletal muscle and decreased proliferative activity is associated with favorable outcome. This upregulation of myogenic differentiation after therapy should not be confused with resolution of the tumor. Patients with embryonal rhabdomyosarcoma exhibit more extensive cytodifferentiation compared with alveolar subtype. Fibrosis generally accompanies extensive differentiation and may account for persistent radiographic abnormalities, which generally prompts second-look surgery.[56] If residual disease is present postoperatively, radiotherapy and chemotherapy are initiated. An algorithm of a current treatment plan is presented in Figure 51-11.

OUTCOME

Overall survival for patients with pelvic rhabdomyosarcoma has increased from approximately 30% to 80% to 90%.[9] This improved survival has been due to the introduction of new chemotherapeutic agents and the use of radiotherapy. As more patients survive, long-term problems appear; these can be secondary to the treatment or to the underlying genetic makeup of the patient. Survival with minimal morbidity is now the main aim of the international rhabdomyosarcoma study groups.

Bladder

Chemotherapy, in particular, therapy with cyclophosphamide, and radiotherapy can cause hemorrhagic cystitis in 30% of patients.[57] Prophylaxis with mesna should be used with cyclophosphamide therapy, but in some cases the acute problem can be severe enough to warrant direct bladder instillation treatment.[58] The long-term outcome of hemorrhagic cystitis on bladder function has not been studied. In addition, radiotherapy can cause urethral strictures and fistulas, which were reported in 2% in IRS.[59]

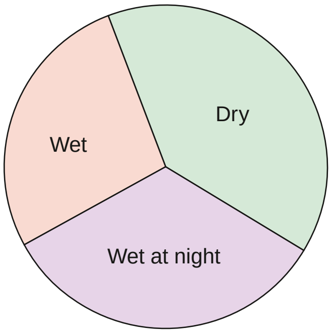

Figure 51-12 Pie graph shows bladder function outcome in a group of 11 patients who underwent formal bladder assessment.

To improve patients' quality of life, the bladder is increasingly being salvaged. In the recent IRS study, of 109 patients with bladder or prostate disease, 50% retained their bladder. Limited follow-up reported that 75% had normal bladder function, and the remainder described some degree of bladder dysfunction, mainly nighttime or daytime incontinence or both.[60] This report may show an overoptimistic view of bladder outcomes, however, because these patients had no formal bladder function review. In a smaller series, 11 of 17 patients were formally studied. Four had completely normal voiding patterns, four were wet at night but dry during the day, and three were wet day and night (Fig. 51-12). Of the seven patients with incontinence, one had a rectourethral fistula, and the remaining six had reduced functional capacity, without detrusor instability. All patients with bladder dysfunction had received external-beam radiotherapy, in contrast to continent patients, none of whom had been exposed to radiation.[61]

Kidney

The kidneys can be damaged by all three therapeutic modalities.[57,62] Chemotherapeutic agents such as ifosfamide are nephrotoxic.[62] Radiation therapy can cause direct renal injury and secondary fibrosis and indirect injury—hydronephrosis resulting from a ureteral stricture after treatment.[57] Finally, surgical reconstruction using bowel increases the frequency of urinary tract infection, ureteric strictures, and stone formation, which all can result in renal damage.

Sexual Function and Infertility

Erectile dysfunction and retrograde ejaculation can occur after cystectomy, prostatectomy, or extensive urethral dissection because of nerve damage at the bladder base. Surgical damage to the vas and seminal vesicles can result in dry ejaculation.[63] When pelvic and retroperitoneal lymph node dissections are performed, retrograde ejaculation and impotence have been reported; animal studies have confirmed that this is secondary to superior hypogastric plexus damage.[64] Ninety percent of patients who had bilateral retroperitoneal lymph node dissections reported sexual dysfunction; this was reduced in patients who underwent unilateral surgery.

Gonadal dysfunction can occur after chemotherapy and radiotherapy. It is more frequent in male patients than in female patients, and younger patients seem to be protected, but not completely excluded. Alkylating agents, such as cyclophosphamide and ifosfamide, can cause gonadal dysfunction that can range from a minor elevation in gonadotropin levels to complete gonadal failure and infertility.[65,66] In a more recent study, sarcoma therapy impaired fertility in approximately two thirds of males, with all male recipients of combined therapy with cyclophosphamide or ifosphamide.[67] These patients require hormonal therapy, although occasional gonadal recovery is observed.

Germ cells are particularly sensitive to radiation therapy; testicular doses greater than 2 Gy are associated with longstanding azoospermia.[59,68] Radiation dosages of 40 Gy are needed to induce ovarian failure in young prepubertal girls.[69] The high incidence of gonadal dysfunction after radiotherapy has led to techniques to avoid irradiating the gonads, including shielding or surgically placing the gonads outside the radiation fields. In patients in whom it is possible, pretreatment germ cell collection and storage should be encouraged so that late treatment–effect infertility can be minimized. The incidence of congenital anomalies and cancer in the children of patients who succeed in having children after treatment does not seem to be greater than in the general population.[70]

Nongenitourinary Complications

Respiratory and cardiac complications can occur with drugs such as cyclophosphamide, methotrexate, and bleomycin.[71] In most patients, pulmonary function is impaired, but few are symptomatic. Chest radiotherapy for lung metastases causes pulmonary fibrosis in adolescents, but in younger children it tends to impede chest wall growth, resulting in reduced lung capacity. Abdominal radiotherapy has been associated with chronic enteritis, strictures, and fistulas that can manifest many years after treatment. In an attempt to keep the bowel out of the pelvis, some surgeons advocate the use of a mesh sling that prevents the small bowel from entering the pelvis during radiotherapy.[72] Increased body mass index, high incidence of hyperlipidemia, increased body fat content, and persistent psychological stress have been reported in rhabdomyosarcoma survivors.[67]

Second Tumors

Long-term studies indicate that survivors of childhood rhabdomyosarcoma have a 2% to 6% chance of developing a second tumor within 10 years of finishing treatment.[73] Bone tumors (osteogenic sarcoma) and acute nonlymphoblastic leukemia were the most common second neoplasms.[72] Most solid tumors occurred within the original radiation field, and most of these patients had an initial tumor size greater than 5 cm.[74] Risk factors for a second malignancy were genetic predisposition, such as Li-Fraumeni syndrome and neurofibromatosis; a high radiation dose (>40 Gy); and high doses of cyclophosphamide.[14]

PROGNOSIS

Prognosis depends on the anatomic site and clinical group. The histologic appearance may also be important, but the histologic subtype and anatomic site are often associated; this has led some investigators to report that the histologic type is not an independent prognostic indicator. The effect of histologic type on outcome is shown in Table 51-2.[8] The 5-year progression-free survival for nonbladder nonprostate genitourinary tumors is 84% compared with 73% for bladder and prostate tumors.[9] Probably the most important factor determining the outcome is the clinical group (Fig. 51-13).[9] Patients with disseminated disease, either residual or metastatic, which accounts for 65% of patients, have a significantly worse outcome.

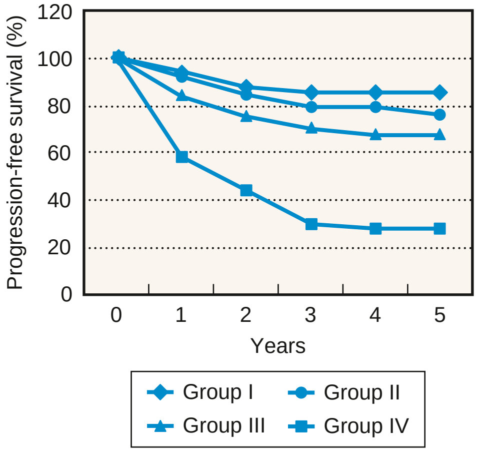

Figure 51-13 Progression-free survival according to clinical group.

CONCLUSION

Enormous advances have been made in the treatment of children with rhabdomyosarcoma. Work now needs to concentrate on two areas. First, improvements are needed in controlling disease in patients who present with disseminated disease. These represent more than half the total patients, and their prognosis is still poor. Second, therapy needs to be continually modified so that organ function can be preserved, specifically the bladder, without affecting survival. There are many exciting areas in which progress may occur; new chemotherapeutic agents are continually being developed, and with an increasing understanding of the molecular biology and growth factor biology that is responsible for rhabdomyosarcoma, is it hoped that more specific therapies will become available. Despite a growing reliance on chemotherapy, surgeons still have an important role to play in the management of children with genitourinary rhabdomyosarcoma.

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CHAPTER 52

TESTICULAR TUMORS

Jonathan H. Ross

Pediatric testis tumors are rare compared with testis tumors occurring postpubertally and with other pediatric urologic tumors, such as Wilms' tumor. Most information on prepubertal testis tumors is obtained from small series and case reports. The introduction of a prepubertal testis tumor registry by the Urologic Section of the American Academy of Pediatrics in 1980 allowed for the accrual of valuable epidemiologic information.[1] Yolk sac tumor is the most common testicular malignancy in prepubertal patients. The appropriate management of yolk sac tumors has been clarified by more recent multicenter trials.[2-7]

The incidence of testis tumors in children is 0.5 to 2 per 100,000 children, accounting for only 1% to 2% of all pediatric tumors.[8] Prepubertal testis tumors are classified by the putative cell of origin. Tumors arising from germ cells include yolk sac tumor, teratoma, and epidermoid cysts. Stromal tumors include juvenile granulosa cell tumor, Leydig cell tumor, Sertoli cell tumor, and mixed or undifferentiated stromal tumors. Gonadoblastomas contain germ cell and stromal elements. Secondary tumors rarely affect the testis, although testicular involvement with acute lymphoblastic/lymphocytic leukemia (ALL) is an important exception. Table 52-1 presents the prevalence of specific primary testis tumors registered in the Prepubertal Testis Tumor Registry. In this registry, yolk sac tumors, which are malignant, account for most prepubertal testis tumors. Compared with testis tumors in adults, however, a higher proportion of pediatric testis tumors are benign. Malignant tumors may be overreported to registries. Reviews of all testicular pathology specimens at specific institutions have found that most prepubertal testis tumors are benign—with teratoma being the most common tumor.[9]

PRESENTATION AND EVALUATION

Testis tumors most commonly manifest as a testicular mass—88% in the Prepubertal Testis Tumor Registry. The mass may be noted by the patient or the patient's family, or detected on a routine physical examination. In the Prepubertal Testis Tumor Registry, 11% of patients had a hydrocele at presentation, which may have been secondary to the tumor or coincidental. The presence of a hydrocele may delay the diagnosis of a testis tumor, and an ultrasound scan should be considered for any boy with a hydrocele in which the testis cannot be palpated. Occasionally, patients present with pain, presumably from an acute bleed into the tumor. Physical examination usually reveals a hard mass in the testicular parenchyma. These masses must be distinguished from benign extratesticular lesions, such as epididymal cysts.

When a testis tumor is suspected, a thorough physical examination is undertaken. Signs of androgenization or feminization should be sought. Metastatic disease is uncommon, and the primary sites—the retroperitoneum and lungs—are unlikely to result in symptoms or physical findings. Rarely, metastases to the bone or central nervous system may occur. Symptoms or signs of involvement at these locations are important in guiding the radiographic evaluation.

The initial radiographic evaluation of children with a suspected testis tumor is limited. Because many prepubertal testis tumors are benign, any metastatic evaluation is usually deferred until tissue confirmation of the tumor's histology is obtained. When a malignancy is suspected (e.g., in children with an elevated alpha-fetoprotein [AFP] level), a computed tomography scan (CT) of the abdomen may be obtained preoperatively. Imaging of the primary tumor is sometimes helpful. Ultrasonography is most often employed. Ultrasound is able to distinguish testicular tumors from benign extratesticular lesions. The extent of testicular involvement can also be determined, which is helpful if testis-sparing surgery is being considered. The ultrasound appearance of specific testis tumors has been described. Ultrasound findings are too inconsistent to allow a definitive diagnosis.

Tumor markers play an important role in the evaluation and follow-up of childhood testis tumors. AFP is the most important tumor marker. It is an albumin precursor synthesized by the yolk sac and fetal liver and gut. AFP is specific for yolk sac tumor. Levels are elevated in 80% to 90% of children with a yolk sac tumor, and AFP has a biologic half-life of approximately 5 days.[10] Elevated levels of AFP preoperatively should preclude consideration of a testis-sparing approach. An important caveat is that AFP levels are normally quite high in infancy (Fig. 52-1). An "elevated" level in a boy younger than 1 year does not rule out the possibility of a benign tumor, such as teratoma.[11] The β subunit of human chorionic gonadotropin is an important marker in adult testis tumors, but this is rarely elevated in children because the histologic types that lead to elevated human chorionic gonadotropin levels are rarely encountered in pediatric testis tumors.

SURGICAL APPROACH

The standard approach to a testis tumor is an inguinal orchiectomy (Fig. 52-2). Through an inguinal incision, the spermatic cord is isolated and clamped with a noncrushing clamp. The testis is delivered into the inguinal incision with the tunica vaginalis intact. When a testis tumor is confirmed by direct palpation, the cord is ligated and divided at the internal ring.

Increasing consideration has been given to performing testis-sparing surgery for benign testicular tumors.[1] This idea is particularly attractive in prepubertal patients because more than one third of tumors are benign in these patients. The preoperative evaluation plays a significant role in patient selection for testis-sparing surgery. An elevated AFP level in a child older than 1 year virtually always reflects the presence of a yolk sac tumor and precludes a testis-sparing approach. In infants and older children with a normal AFP, the likelihood of a benign tumor is considerable. This is also true in boys presenting with androgenization. For these patients, an inguinal exploration should be considered so that testis-sparing surgery may be performed if a benign histology is confirmed (Fig. 52-3). The initial approach is the same as for an inguinal orchiectomy. When the testis is delivered into the inguinal incision (the cord having been clamped with a noncrushing clamp), the field is draped off with towels, and the tunica vaginalis is opened. The tumor is excised with a margin of normal parenchyma or enucleated and sent for frozen section. If a benign histology is confirmed, the testicular defect is closed with chromic suture, and the testis is returned to the scrotum. If a malignancy is detected, or the frozen section is nondiagnostic, an orchiectomy is performed. Reports from small series suggest that this approach is safe and is effective in preserving testicular tissue.[12]

After orchiectomy, some children with testicular tumors require additional evaluation and therapy. The type of adjunctive management selected depends on the histology of the primary tumor and the results of radiographic and biochemical studies. The intensity of follow-up also depends on the malignant potential of the primary tumor.

YOLK SAC TUMOR

Yolk sac tumor accounts for nearly all malignant prepubertal testis tumors. Yolk sac tumors have been referred to by many other names, including endodermal sinus tumor, orchioblastoma, juvenile embryonal carcinoma, mesoblastoma vitellinum, clear cell adenocarcinoma, extraembryonal mesoblastoma, and archenteronoma.[8] Most patients present younger than 2 years of age. Yolk sac tumor is a solid tumor that is yellow to pale gray in color.[13] Various histologic patterns may occur. In some cases, the tumor is indistinguishable from embryonal carcinoma. Positive staining with AFP strongly supports the diagnosis of a yolk sac tumor, however. Other features that may be present include glomeruloid (or Schiller-Duval) bodies and embryoid bodies. Glomeruloid bodies and embryoid bodies are clusters of cells resembling the structures for which they are named. Hyaline bodies, which may be intracellular or extracellular, are also characteristic of yolk sac tumor, although they may be seen in other tumors as well.

Table 52-1 **Prevalence of Tumor Types among 395 Primary Testis Tumors in the Prepubertal Testis Tumor Registry**

	%
Germ cell tumors	88
Yolk sac	62
Teratoma	23
Epidermoid cysts	3
Stromal tumors	10
Sertoli	2
Juvenile granulosa cell tumor	2
Leydig	1
Mixed/unspecified stromal	5
Gonadoblastoma	1

Metastatic evaluation of yolk sac tumors includes a CT scan of the abdomen and pelvis to rule out retroperitoneal lymph node or hepatic metastases, and a chest x-ray or chest CT scan to rule out pulmonary metastases. Bone and brain metastases are rare. Bone scans and head CT scans are obtained only when there is clinical suspicion of metastases at these sites. Serum AFP level is also measured postoperatively. Its half-life is approximately 5 days, and a persistent elevation of AFP after orchiectomy suggests the presence of metastatic disease. AFP levels of 50,000 ng/mL can occur in normal infants, however, and levels greater than 50 ng/mL can occur in children 6 months of age.[14] Serial measurements are particularly important in small children.

A tumor-node-metastasis (TNM) staging system exists for testis tumors, but its applicability to pediatric tumors is limited because of the infrequent employment of retroperitoneal lymph node dissection (RPLND) in these patients. Several other systems have been proposed, the simplest of which segregates patients into three stages.[15] Stage I patients have tumor confined to the testis with a negative metastatic evaluation and a normalization of AFP postoperatively. Stage II patients have retroperitoneal disease detected by radiographic studies or RPLND, a persistent elevation of AFP postoperatively, or both. Stage III patients have metastatic disease beyond the retroperitoneum. Approximately 80% of children with yolk sac tumors have stage I tumors.

Historically, RPLND was the most common form of adjunctive therapy for the treatment of yolk sac tumors. A standard RPLND is accomplished through a midline or transverse abdominal incision. Complete excision of all lymphatic tissue from the renal hila to 2 cm beyond the bifurcation of the common iliac arteries is accomplished. The lateral margins of dissection are the ureters, and the great vessels are completely skeletonized throughout.

Modified templates limiting the contralateral dissection and nerve-sparing techniques have been described in adults in an attempt to minimize the morbidity of the dissection, particularly anejaculation. For right-sided tumors, a modified template dissection is limited medially by the anterior surface of the aorta. Below the inferior mesenteric artery, dissection is limited medially by the right common iliac artery, preserving the hypogastric plexus. The modified template for a left-sided tumor

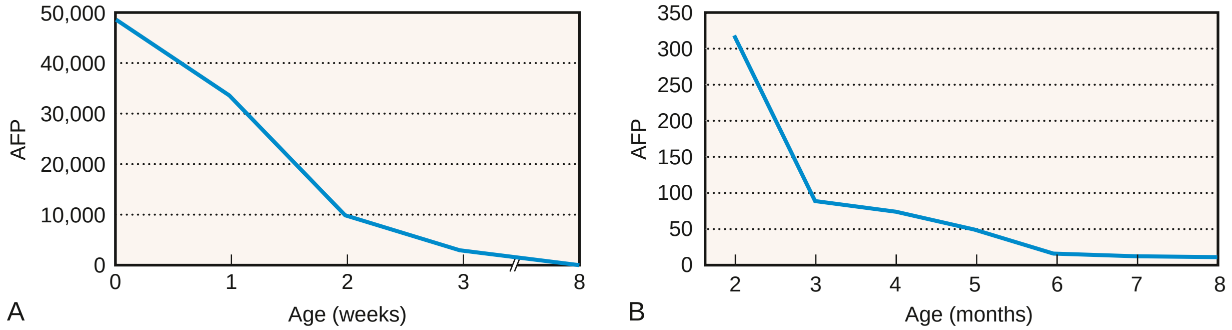

Figure 52-1 Alpha-fetoprotein (AFP) levels (in ng/mL) as a function of age in normal infants. **A,** During the first 8 weeks of life. **B,** From 2 to 8 months of age. (Data from Wu JT, Book L, Sudar K. Serum alpha-fetoprotein [AFP] levels in normal infants. *Pediatr Res.* 1981;15:50.)

is limited medially by the anterior surface of the inferior vena cava. Below the inferior mesenteric artery, dissection is again limited medially by the left common iliac artery. The efficacy of these modified techniques has not been clarified in children.

With the widespread use of AFP to detect occult metastases and improvements in multiagent chemotherapy, the reliance on RPLND to diagnose and treat metastatic disease in prepubertal patients has waned. Although some series suggested improved survival with RPLND, the studies were uncontrolled, and most patients who "benefited" had no histopathologic evidence of disease in the resected nodes.[16] Theoretically, RPLND is less beneficial for children than for adults because yolk sac tumors in children have a predilection for hematogenous spread, with only a few metastases being limited to the retroperitoneum. A review of the Prepubertal Testis Tumor Registry found that metastases were limited to the retroperitoneum in only 32% of patients with metastatic disease, whereas metastatic disease in 46% of these patients occurred at hematogenous sites *without* retroperitoneal involvement.[17] The operative morbidity of RPLND in children is significant, including wound complications, bowel obstruction, chylous ascites, and anejaculation as adults owing to injury to the sympathetic nerves.[16] Currently, retroperitoneal surgery is limited to excisional biopsy of retroperitoneal masses in patients with a normal AFP and excisional biopsy of residual masses after chemotherapy—both rare events.

Chemotherapy is very effective in treating metastatic yolk sac tumor. The most commonly used regimens include cisplatin or carboplatin in combination with other agents, such as etoposide and bleomycin. Because children with metastatic disease often have multiple sites of spread, chemotherapy is particularly appropriate for these patients.

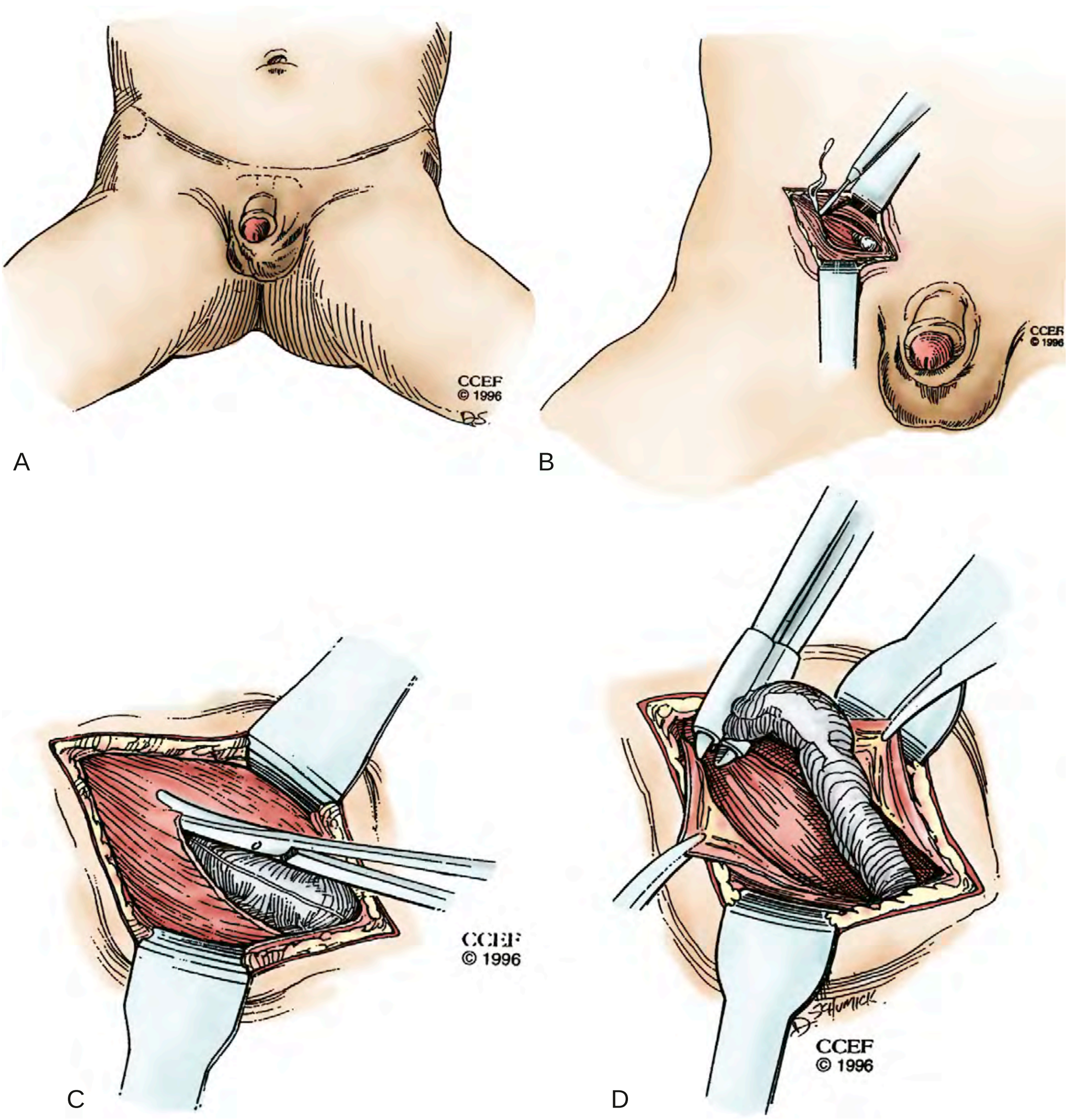

Figure 52-2 Technique of inguinal orchiectomy. **A,** A transverse incision is made in the inguinal crease midway between the anterior superior iliac spine and the pubic tubercle. **B,** Electrocautery is used to divide the Scarpa fascia down to the level of the external oblique fascia. **C,** The external oblique fascia is divided in the direction of its fibers directly over the spermatic cord. **D,** After the cord has been elevated, a noncrushing clamp is placed at the level of the internal ring.

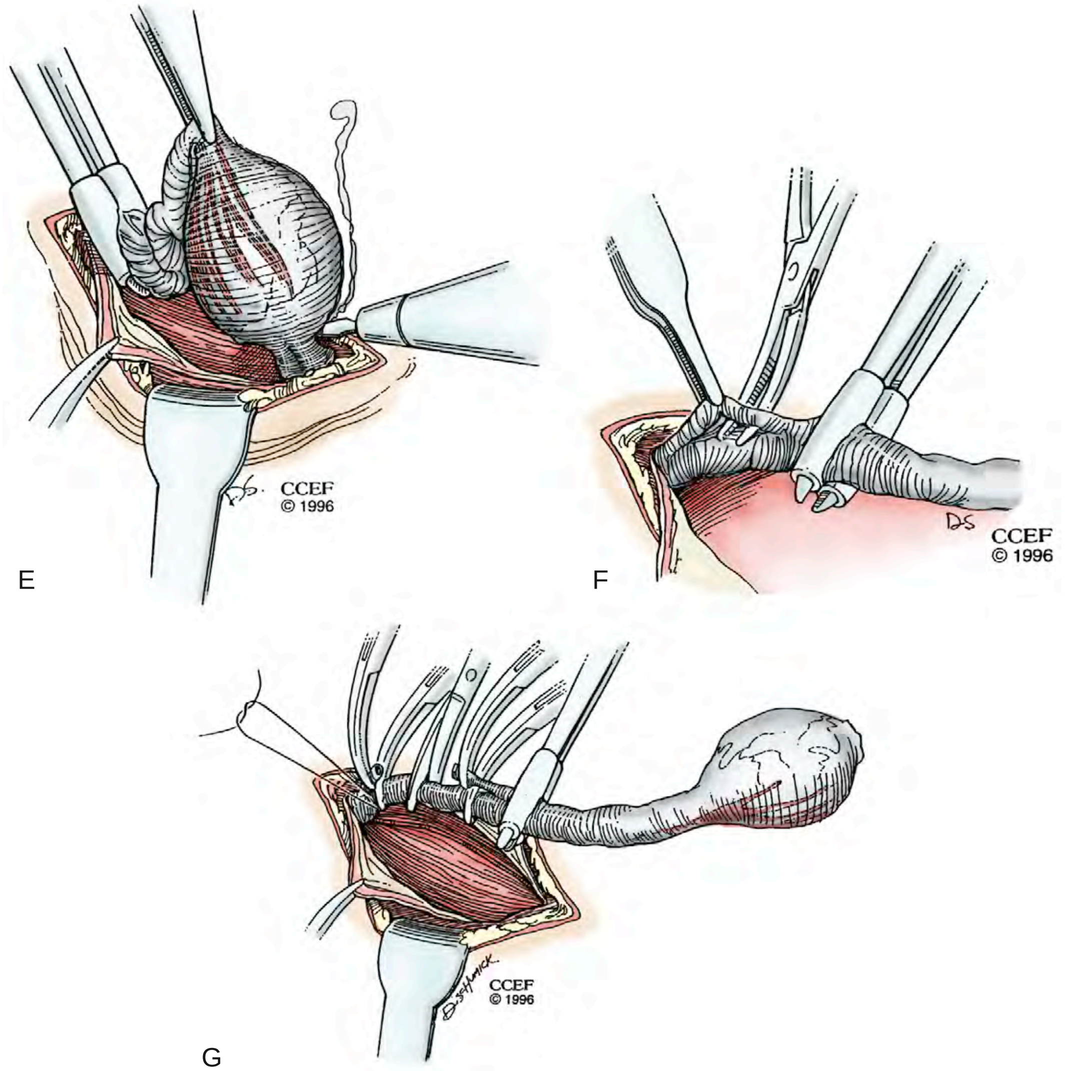

Figure 52-2 cont'd, **E,** The testis is delivered into the wound, and the gubernaculum is divided sharply using electrocoagulation. **F,** After the intratesticular tumor has been confirmed, the cord is divided proximal to the crushing clamp. It is divided by isolating the vas from the spermatic vessels and dividing the vas separately. **G,** The vas has been divided, and the spermatic vessels are clamped. The cord is sharply divided. (Reprinted with the permission of The Cleveland Clinic Foundation.)

Radiation is not a standard form of treatment for metastatic yolk sac tumor. Although yolk sac tumor is radiosensitive, the doses required when radiation is used as a primary therapy are prohibitively toxic.[15] Lower doses of radiation may play a role in combination with surgery and chemotherapy for high-risk patients.

As with adult germ cell tumors, the selection of adjuvant therapy for yolk sac tumor depends on the stage of the tumor. The trend in managing stage I tumors is toward observation. Most series reported during the 1990s have found no survival advantage to adjuvant therapy in this group (Table 52-2).[3,5,7,18,19] The recurrence rate for patients with stage I tumor managed by observation is approximately 15%, and virtually all of these patients can be salvaged with chemotherapy. Chemotherapy may be considered in patients with a normal AFP before orchiectomy who cannot be reliably followed biochemically. Patients with stage I tumor are generally observed closely without adjuvant therapy. Patients are evaluated 1 month after orchiectomy with a CT scan of the abdomen and pelvis, a chest x-ray, and a serum AFP. Serum AFP is measured monthly for 6 months, then every 3 months from 6 months to 2 years. A chest x-ray and abdominal/pelvic CT scan are obtained every 3 months for the first year, and every 6 months during the second year. Recurrent disease is usually treated with chemotherapy, even if it seems to be limited to the retroperitoneum. If the patient remains disease-free for 2 years, he is almost certainly cured, although annual follow-up is continued.

Patients with a negative metastatic evaluation, but a failure of the AFP to normalize, are generally treated with chemotherapy. A "normal" AFP in infants may be quite high. Patients with positive lymph nodes on CT scan are also treated with chemotherapy, although consideration may be given to performing a modified RPLND in the presence of minimal retroperitoneal disease and a normal AFP. RPLND should also be considered when retroperitoneal disease is not responding to chemotherapy or for a persistent mass after chemotherapy when the AFP level has normalized. Some of these residual masses contain only necrotic tumor and calcifications.[10]

Chemotherapy is the mainstay of treatment for patients with hematogenous metastases. Chemotherapy with second-line

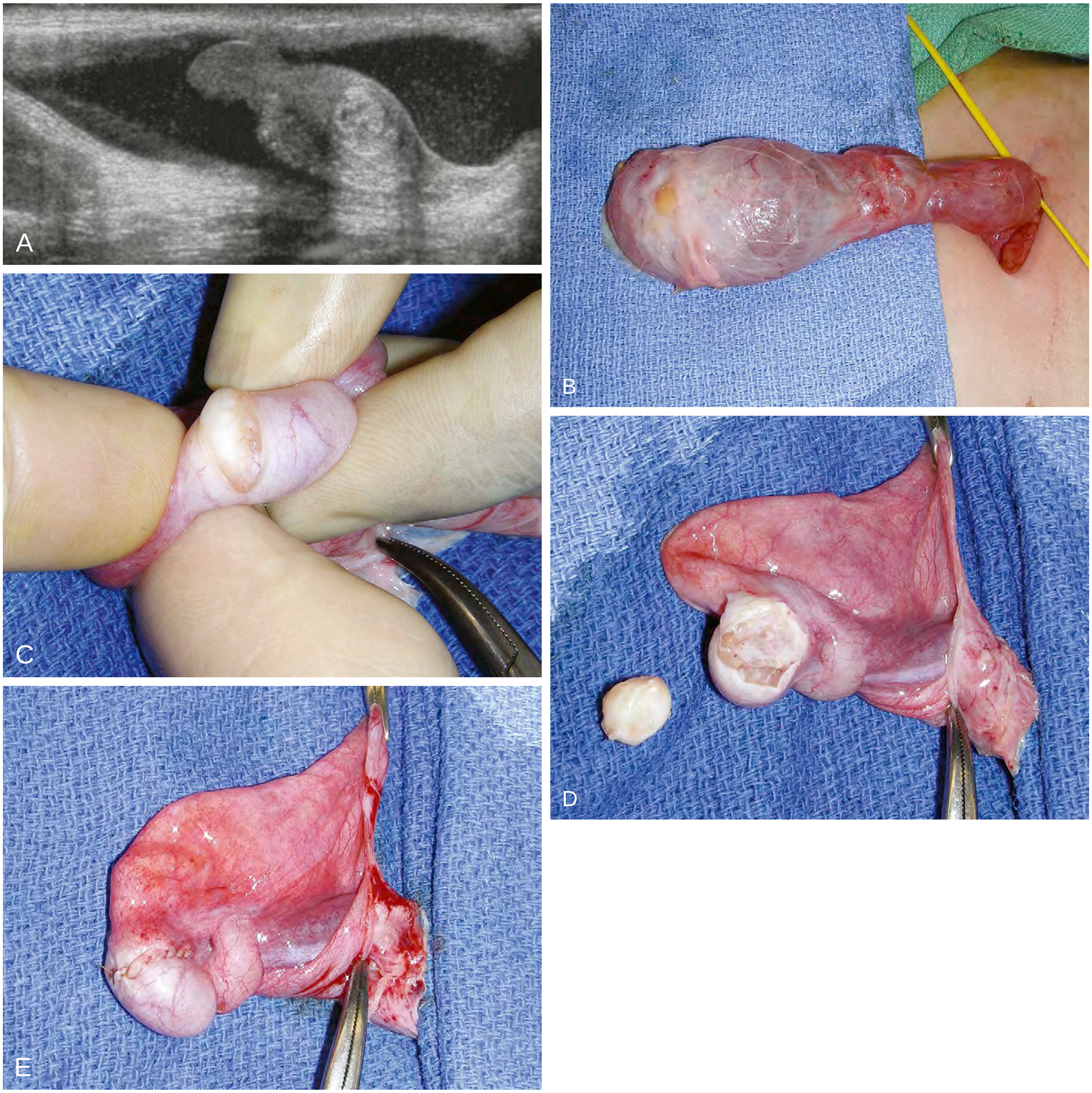

Figure 52-3 Testis-sparing surgery. **A,** Scrotal ultrasound scan in a 4-year-old boy with a hydrocele reveals a hyperechoic testicular mass. Alpha-fetoprotein was normal. **B-E,** The spermatic vessels were controlled through an inguinal incision, the tumor was enucleated, and when the frozen section revealed an epidermoid cyst, the testicle was closed and replaced in the scrotum.

agents should be used for patients failing to respond to standard agents. Surgical excision and radiation should also be considered for patients with limited sites of metastatic disease who fail to respond to chemotherapy.

TERATOMA AND EPIDERMOID CYST

Teratoma is the most common benign prepubertal testis tumor, accounting for 23% of primary testis tumors in the Prepubertal Testis Tumor Registry and most of all tumors in series reported by specific centers. The median age of presentation is 13 months, with several patients presenting in the neonatal period.[20] Histologically, teratomas consist of tissues representing the three germinal layers—endoderm, mesoderm, and ectoderm. The presence of cysts on ultrasonography suggests the diagnosis, but is neither sensitive nor specific.

Epidermoid cysts are benign tumors accounting for approximately 3% of primary testicular tumors. They are composed entirely of keratin-producing epithelium. They are distinguished from dermoid cysts, which contain skin and skin appendages, and from teratomas, which contain derivatives of other germ cell layers.[13] On ultrasound, most epidermoid

Table 52-2 **Results of Four Large Multicenter Studies of Prepubertal Malignant Germ Cell Tumors of the Testis**

	No. patients	Stage I Tumors (%)	Recurrence of Stage I Tumors on Observation (%)	Survival for Stage I Tumors (%)	Survival for Patients with Residual Disease/ Metastases (%)
United Kingdom's Children's Cancer Study Group[5]	62	68	5	100	100
German Cooperative Studies[2]	110	95	15	100	80
U.S. Pediatric Intergroup Study[3,4,7]	94	67	17	100	100
Italian Cooperative Study[6]*	36	72	19	100	100
Total	*302*	*78*	*14*	*100*	*98*

*Includes six patients older than 10 years.

cysts appear as discrete intratesticular masses with areas of increased echogenicity corresponding to the keratin debris or peripheral calcification.[21] Other areas of decreased echogenicity may also be present corresponding to regions of the cyst not filled with debris. These findings vary, however, and an epidermoid cyst may appear as a homogeneous solid mass.[22] The primary value of ultrasonography is in characterizing the mass as intratesticular and in excluding abnormalities elsewhere in the testis that would necessitate total orchiectomy.

Teratomas and epidermoid cysts are universally benign in prepubertal children. Testis-sparing surgery is a reasonable consideration for these patients.[22-24] Frozen sections should be obtained to confirm the diagnosis. In older children with teratoma, the normal testicular parenchyma must be carefully evaluated. If there is histologic evidence of pubertal changes, an orchiectomy should be performed because teratomas are potentially malignant in postpubertal boys. Although epidermoid cysts are benign in children and adults, there have been reports of teratoma being present on the final pathologic evaluation when an epidermoid cyst was the frozen section diagnosis.[22]

Whether biopsies of surrounding testicular parenchyma are necessary is unclear.[23,25,26] Although 88% of testes removed for adult teratoma contain areas of intratubular germ cell neoplasia, this has generally not been the case for epidermoid cysts or for pediatric teratoma.

For patients with epidermoid cyst and prepubertal patients with teratoma, no radiographic studies or follow-up for the development of metastatic disease is required. Because of the potential for malignancy, postpubertal patients with teratoma should be evaluated and followed on the same protocol as adults with other malignant germ cell tumors.

GONADAL STROMAL TUMORS

Stromal testis tumors are rare in children, and there are no large series to guide their management. Anecdotal reports and small series in the literature offer some experience, however, on which to base therapy.[27]

Leydig Cell Tumor

Leydig cell tumors are universally benign in children.[8,27] The children usually present between 5 and 10 years of age with precocious puberty. Presenting symptoms include an early growth spurt, prominent external genitalia, erections, pubic and axillary hair, facial hair, acne, and deepening of the voice. Although feminization (particularly gynecomastia) is common in adults, it is rare in children and, when present, is usually superimposed on the virilizing signs. Other causes of precocious puberty include central nervous system lesions, adrenocortical carcinoma, and congenital adrenal hyperplasia (CAH). In the presence of a testicular mass, a Leydig cell tumor is the most likely diagnosis. An elevated testosterone level with low or normal follicle-stimulating hormone and luteinizing hormone levels is consistent with a Leydig cell tumor. Normal levels of 17-hydroxyprogesterone exclude the diagnosis of CAH. Because virilization may manifest before a tumor is palpable, all boys with precocious puberty and no obvious cause should undergo an ultrasound scan of the testicles to rule out a small tumor.

Leydig cell tumors may be treated by orchiectomy or testis-sparing excision. Persistence of androgenic effects may be due to a contralateral tumor, but this is rare in children. Because Leydig cell tumors are sometimes difficult to detect on physical examination, an ultrasound scan may be necessary to rule out a contralateral tumor. Even after successful removal of a solitary tumor, however, androgenic changes are not completely reversible, and some children may proceed through premature puberty owing to activation of the hypothalamic-pituitary-gonadal axis.

Sertoli Cell Tumor

Sertoli cell tumors account for only 2% of primary prepubertal testis tumors. They are usually well circumscribed and often lobulated. Cysts are common. In children, Sertoli cell tumors must be distinguished from juvenile granulosa cell tumors. The latter typically display prominent follicular differentiation, whereas neoplastic Sertoli cells are characteristically arranged in tubules or infiltrate preexisting seminiferous tubules.[13]

A review of 60 cases of Sertoli cell tumors reported only 4 cases in patients younger than 20 years; the youngest patient was 15 years old.[28] Approximately 10% of adult Sertoli cell tumors are malignant. These malignant tumors are usually characterized by large tumor size, areas of necrosis, vascular invasion, cellular atypia, and increased mitotic activity. In contrast to general series dominated by adult patients, the median age of patients in the Prepubertal Testis Tumor Registry was 6 months (range 4 months to 10 years). There were no reports of metastatic disease. Sertoli cell tumors are usually hormonally inactive in children, although they occasionally may cause gynecomastia or isosexual precocious puberty.[29] Although all reported cases to date have been benign in children younger than 5 years, there have been a few cases of malignant Sertoli cell tumors in older children.[30,31]

Orchiectomy is sufficient treatment in infants, although a metastatic evaluation could be considered in infants with worrisome histologic findings. Older children should undergo an abdominal CT scan and chest x-ray to rule out metastases. When metastatic disease is present, aggressive combination treatment including RPLND, chemotherapy, and radiation therapy should be considered.

The large cell calcifying Sertoli cell tumor is a clinically and histologically distinct entity with a higher incidence of multifocality and hormonal activity.[8,32,33] These tumors are composed of large cells with abundant cytoplasm and varying degrees of calcification ranging from minimal amounts to massive deposits. Although standard Sertoli cell tumors are more common in adults, large cell calcifying Sertoli cell tumors are found predominantly in children and adolescents. Most manifest with a testicular mass. Approximately one fourth of patients have bilateral and multifocal tumors. The presence of calcifications results in a characteristic ultrasound appearance including multiple hyperechoic areas.

Approximately one third of patients with large cell calcifying Sertoli cell tumor have an associated genetic syndrome or endocrine abnormality or both. The two syndromes most commonly associated with large cell calcifying Sertoli cell tumor are Peutz-Jeghers syndrome and Carney syndrome. Peutz-Jeghers syndrome is an autosomal dominant disorder consisting of mucocutaneous pigmentation and hamartomatous intestinal polyposis. Features of Carney syndrome include myxomas of the skin, soft tissue, and heart; myxoid lesions of the breast; lentigines of the face and lips; cutaneous blue nevi; Cushing syndrome; pituitary adenoma; and schwannoma. Awareness of this familial syndrome is important because patients and their first-degree relatives are at risk for the potentially lethal associated entities.

Although they are occasionally malignant in adults, large cell calcifying Sertoli cell tumors have been universally benign in patients younger than 25 years. Orchiectomy is sufficient treatment for children.

Juvenile Granulosa Cell Tumor

Juvenile granulosa cell tumor is a stromal tumor bearing a light microscopic resemblance to ovarian juvenile granulosa cell tumor. Granulosa cell tumors occur almost exclusively in the first year of life, most in the first 6 months. Of 22 newborn tumors in the Prepubertal Testis Tumor Registry,[20] 6 were juvenile granulosa cell tumors, 6 were yolk sac tumors, and 6 were unspecified stromal tumors. Structural abnormalities of the Y chromosome and mosaicism are common in boys with juvenile granulosa cell tumor.[30] Several cases have been described in association with ambiguous genitalia.[34] These tumors are hormonally inactive and benign. Although these children should undergo chromosomal analysis, no treatment or metastatic evaluation is required beyond orchiectomy or tumor enucleation.[35]

Mixed or Undifferentiated Stromal Tumors

Histologically, "mixed" or "undifferentiated" stromal tumors consist of areas of gonadal stromal neoplasia and undifferentiated regions of spindle cells that may exhibit a high mitotic rate. These stromal tumors have an epidemiology similar to that of granulosa cell tumors. Although some of these tumors have histologic characteristics commonly associated with malignancy, most are benign. There are inadequate data in the literature to formulate rigid guidelines for managing these tumors. Although histologic features may not correlate with invasive or metastatic potential, a high index of suspicion is appropriate when there are numerous mitotic figures, the tumor is poorly differentiated, or local invasion is present in the primary tumor.[27] Although aggressive behavior has not occurred in young infants, there are reports of such behavior in older children. Because orchiectomy cures most of these patients, RPLND and adjuvant therapy are probably inappropriate in the absence of radiographic evidence of metastatic disease. Given the uncertainty, however, postoperative evaluation and follow-up for the development of metastatic disease seem prudent.

Gonadoblastoma

Gonadoblastomas contain germ cells and stromal cells. Usually three distinct elements are present: (1) large germ cells resembling seminoma, (2) sex cord nongerminal elements such as Sertoli or granulosa cells, and (3) stromal elements such as Leydig cells.[36] Gonadoblastomas occur more frequently in postpubertal patients, but they may be seen in children. Gonadoblastoma occurs almost exclusively in dysgenetic gonads, usually in association with an intersex disorder. Dysgenetic gonads are gonads that have failed to develop normally and are composed of gonad-type fibrous tissue. They are also termed *streak gonads*. Although the nomenclature is inconsistent, dysgenetic gonads may contain some primitive ovarian structures. Conversely, when partial differentiation along testicular lines is present, the gonad is referred to as a *dysgenetic testis*. Gonadoblastoma is more likely to occur in dysgenetic gonads or dysgenetic testes in patients with a Y chromosome or evidence of some Y chromatin. Gonadoblastomas occur in 3% of patients with true hermaphroditism, and 10% to 30% of patients with mixed gonadal dysgenesis or pure gonadal dysgenesis and an XY karyotype.[37,38] They also occur commonly in the dysgenetic testis syndrome.

Gonadoblastomas are usually asymptomatic and often detected incidentally when dysgenetic gonads are removed. Virilization has been associated with some of these tumors, however. Forty percent of gonadoblastomas are bilateral.[37] Although gonadoblastomas are benign, overgrowth of the germinal components leading to a dysgerminoma (also known as seminoma) occurs in 50% of cases.[38] Approximately 10% develop overtly malignant tumors. Although most invasive tumors associated with intersex occur in young adulthood, there are several reports in children as well.[38] Intraepithelial germ cell neoplasia may be identified in many of these gonads and is associated with germ cell tumors.

Gonadoblastomas are treated by orchiectomy. Any dysgenetic gonad in a child with a Y chromosome should be removed prophylactically in infancy or early childhood. Tumors are much less likely in patients who lack a Y chromosome, such as patients with Turner syndrome or XX patients with pure gonadal dysgenesis. When malignant degeneration is present, a metastatic evaluation and appropriate follow-up are indicated. These tumors are radiosensitive and have a favorable prognosis. If unfavorable elements such as choriocarcinoma or embryonal carcinoma are present, the outlook is poor.

Five percent to 10% of patients with androgen insensitivity syndrome develop germ cell tumors.[38] Patients with androgen insensitivity syndrome do not have dysgenetic gonads and are not prone to gonadoblastoma. Similar to otherwise normal boys with undescended testicles, the tumors associated with androgen insensitivity syndrome are most often seminomas occurring postpubertally. All standard types of postpubertal germ cell tumors may occur, however. Patients with androgen insensitivity syndrome may also develop Sertoli cell adenomas, which are benign hamartomatous nodules composed of multiple small tubules lined by prepubertal-type Sertoli cells.

HYPERPLASTIC NODULES IN CONGENITAL ADRENAL HYPERPLASIA

Adrenal rest tissue can be found along the spermatic cord and in the testicular hilum of newborns. This tissue generally regresses in infancy, but may persist in boys with CAH. Stimulation of the tissue by high levels of adrenocorticotropic hormone can lead to multiple, usually bilateral, nodular growths in the testes.[39-41] Some patients with milder unrecognized forms of CAH may present with testicular masses. In such patients who present with precocious puberty, the testicular masses could be misinterpreted as Leydig cell tumors. The nodules of CAH are similar histologically to Leydig cell tumors, potentially perpetuating the error even after excision. Any child presenting with precocious puberty and a testicular mass should undergo an endocrinologic evaluation, including measurement of serum 17-hydroxyprogesterone, to distinguish these two entities.

The hyperplastic nodules of CAH are benign. Thirty percent of boys with CAH may have sonographically identifiable testicular lesions, although most are not apparent on physical examination.[42] Many, but not all, of these nodules resolve or significantly reduce in size in response to steroid replacement or an increase in steroid therapy. If this occurs, the patient may be followed safely with serial examinations or ultrasonography or both.[43] Because any testicle may develop a true testicular tumor, a biopsy specimen should be obtained of any nodules that fail to respond to adjustments in steroid replacement. Testicular nodules associated with CAH are typically multifocal, including extratesticular nodules, and are composed of cells with vesicular nuclei in a cordlike arrangement similar to the adrenal cortex. Reinke crystals, pathognomonic of Leydig cell tumors, should be absent. Orchiectomy should be avoided, unless the biopsy specimen reveals some lesion other than an adrenal rest nodule. Large tumors that fail to regress may be enucleated.[43,44]

LEUKEMIA

Secondary malignancies of the testicle are rare. The most important is ALL. Only 2% of boys with ALL have overt clinical evidence of testicular involvement at diagnosis.[45] This involvement is usually reflected in firm diffuse enlargement of one or both testicles and portends a poorer prognosis. Subclinical (i.e., microscopic) involvement of the testes is present in approximately 20% of patients with ALL at the time of diagnosis.[46] Patients with T-cell leukemia and patients with higher leukemia cell burdens may be particularly prone to testicular involvement. Most patients with microscopic testicular involvement achieve a complete remission, however, after modern standard chemotherapy.[47] Conversely, some patients without evidence of testicular involvement at diagnosis ultimately relapse in the testicles. Pretreatment testicular biopsy is unnecessary because it does not predict patients who are prone to have persistent or relapsing disease at that site.

Relapse in the testicles after chemotherapy used to occur in approximately 10% of patients. The testis may represent a protected site from chemotherapy, and be more prone to relapse. With modern ALL chemotherapy, however, testicular relapse occurs in less than 1% of cases.[48] Postchemotherapy biopsy in the absence of physical findings (to rule out occult persistence of tumor in the testes) is no longer routine. The few patients with testicular enlargement persisting or occurring after chemotherapy should undergo biopsy to confirm testicular ALL. Most of these patients are found to have relapsed at other sites as well and require additional intensive systemic chemotherapy to prevent ultimate clinical hematologic relapse.[49] Radiation to the testicles is also required. In the rare cases of unilateral testicular relapse, consideration should be given to orchiectomy. This could allow lower doses of radiation to the remaining testicle and, ultimately, better endocrine function than would occur with higher doses of radiation to both testicles if the affected testicle were left in place. Most patients with testicular relapse after chemotherapy can be salvaged and attain long-term survival. Relapse during chemotherapy portends a more dire outcome.

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CHAPTER 53

ADRENAL TUMORS IN CHILDREN

Gordon A. McLorie and Darius J. Bägli

EPIDEMIOLOGY OF ADRENAL TUMORS

Adrenal tumors in children constitute one of the most common tissue sites for the origins of neoplasia in infancy and childhood (neuroblastoma). In addition, neuroblastoma is a tumor that continues to capture the imagination of biologists, and it remains in the forefront of studies of the fundamental nature of the biology of neoplasia in children.

Neuroblastoma is the most common adrenal tumor of infancy and young childhood, and the functional adrenal tumors present the clinician with some of the most visible manifestations of the hormone-producing tumors of the endocrine system. These tumors include tumors that produce glucocorticoids, tumors that produce sex hormones, and, in older children, adrenal medullary pheochromocytomas, which produce catecholamines. Benign adrenal tumors include adrenal cysts and benign adenomas. The incidence of neuroblastoma in children younger than 15 years is 10.5 per 1 million per year. This constitutes the largest percentage of childhood solid tumors (8% to 10%). There are no geographic or racial propensities. The peak age of incidence is 0 to 4 years, with a median age of 23 months, making neuroblastoma the most common solid tumor in young children. More than 90% of tumors occur in patients younger than 10 years.

Advances in ability to analyze the DNA within the neuroblastoma tumor cells and peripheral blood cells of patients have allowed physicians to distinguish at the genetic level tumors that appear histologically similar. It is now possible to recognize neuroblastoma tumors with a markedly different prognosis (differences in the N-*myc* gene content) and tailor therapy accordingly.[1]

The fact that neuroblastoma manifests in infancy has led to neonatal screening programs. Two studies, in Japan and in Quebec, Canada, have shown that the biologic potential of tumors occurring in the newborn period is substantially different from that of tumors occurring sporadically. This feature has mirrored Cushing's description of the change in potential biologic activity from a malignant tumor to a benign one.[2] These insights into neonatal tumor behavior, in addition to showing variety in the biology of neuroblastomas, have led to a thesis that tumors detected during neonatal screening programs are tumors that have a natural propensity for spontaneous resolution. The conclusion from these studies is that mass screening for neuroblastoma, although feasible, is unlikely to alter the course of patients destined to die of the disease.[3]

No definite environmental causative factors have been identified for neuroblastoma. Chemical carcinogens continue to be implicated in childhood malignancies, although none are specific to neuroblastoma.[4]

PATHOLOGY

Tissue Pathology

The histopathologic features that define the malignant potential of adrenal tumors in children are unique; the diagnostic Homer-Wright pseudorosettes that consist of eosinophilic neutrophils surrounded by neuroblasts occur in only half of the cases.[5] The presence of associated neuropil pigmented neuritic processes is pathognomonic for neuroblastoma. The other type of cell highly characteristic of neuroblastoma is the Schwann cell, which may be recruited into the tumor and constitutes the so-called schwannian stroma, which makes up the mesenchymal component of the tumor. The degree of histologic differentiation is classified according to various schemes, but the most popular was developed by Shimada and colleagues[6] and has been revised by Joshi and associates[7] (Table 53-1), and a combination of the two is the basis of planned prospective trials.

Molecular Pathology

Molecular understanding of neuroblastoma has identified several features of the disease that may aid in all aspects of its management, including diagnosis, natural history, prognostic stratification, and selection of treatment. Newer techniques include analyses of nuclear and chromosomal material and neuronal phenotyping through assessment of various neuron-associated growth factors. Although karyotyping has identified specific chromosomal abnormalities (see later), analysis of DNA ploidy has also provided significant information. Paradoxically, neuroblastomas of the hyperdiploid variety are more likely to respond favorably to chemotherapy, whereas diploid or near-diploid tumors are associated with higher stage disease (including unresectable tumors), a poorer prognosis, a lower response to chemotherapy, and recurrence or progression.[8-11]

An accepted genetic marker for neuroblastoma has been amplification of the *MYCN* (or N-*myc*) proto-oncogene.[12,13] The association between *MYCN* amplification and high-grade,[14] advanced-stage disease at presentation; rapid progression; and an overall poor prognosis has become well established. An etiologic relationship between *MYCN* and neuroblastoma was tested in the late 1990s by two complementary studies. *MYCN* gene amplification is present in approximately 40% of patients with advanced-stage III or IV disease compared with less than 10% in low-stage patients. Chan and coworkers[15] presented data supporting the concept that *MYCN* expression is directly involved in the cellular events of neuroblastoma progression. Conversely, in the subgroup of patients who did well with normal *MYCN* gene expression, Mycn protein levels were undetectable.

Deletions of chromosome 1 and gains in chromosome 17 have been shown to carry strong prognostic information in advanced neuroblastoma. A landmark report from a collaborative group in Europe has shown a powerful association between gains in chromosome 17q and an adverse neuroblastoma outcome.[16] The gain of 17q was linked to the loss of 1p.[16] Most significantly, in univariate and multivariate analyses, 17q gain was independently predictive of a poor outcome (30.6% 5-year survival with 17q gain versus 86% 5-year survival without 17q gain).[16]

A long-standing notion in tumorigenesis states that transformation (neoplasia) is the result of aberrant differentiation

Table 53-1 Histopathologic Classifications of Shimada and Joshi

Histopathologic Features and Ages	Prognosis
Shimada	Favorable
Stroma rich, all ages, no nodular pattern	
Stroma rich, all ages, nodular pattern	
Stroma poor, age 1.5-5 yr, differentiated, MKI <100	
Stroma poor, age <1.5 yr, MKI <200	
Shimada	Unfavorable
Stroma poor, age <1.5 yr, MKI >200	
Stroma poor, age >5 yr	
Stroma poor, age 1.5-5 yr, undifferentiated	
Stroma poor, age 1.5-5 yr, differentiated, MKI >100	
Joshi	
Grade 1,* all ages; grade 2, † <1 yr	
Grade 2, age >1 yr; grade 3, ‡ all ages	

*Grade 1—low mitotic rate (<10 mitotic figures per 10 high-power fields) and calcification present.

†Grade 2—either low mitotic rate or calcification present.

‡Grade 3—neither low mitotic rate nor calcification present.

MKI, mitosis-karyorrhexis index (number of mitoses and karyorrhexes per 5000 cells).

Adapted from Brodeur GM, Castleberry RP. Neuroblastoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology.* Philadelphia: Lippincott; 1997:771.

pathways leading away from the normal cell phenotype. As a result, neuroblastoma may represent an aberration of normal neuronal development. Several neuronal differentiation markers have been investigated in this disease, including chromogranin A, neuropeptide Y, and receptors for neurotrophins such as nerve growth factor. Neuropeptide Y is detectable in abundance in the serum of neuroblastoma patients and may be useful in following the tumor burden before and after therapy.[17] In tumor tissue, it reaches its highest levels in poorly differentiated neuroblastoma compared with ganglioneuroblastoma or ganglioneuroma.[17] Conversely, chromogranin A derivatives may become useful markers of more favorably differentiated tumors.[18]

Neurotrophic factors are involved in the differentiation of neural tissues. One family of neurotrophin receptors, the tyrosine kinase receptors *Trk-A*, *Trk-B*, and *Trk-C*, may lend some understanding to neuroblastoma biology. It seems that *Trk-A* gene expression is associated with a favorable outcome, yielding its highest expression in more well-differentiated tumors.[19,20] *Trk-A* levels are *inversely* correlated with *MYCN* gene expression.[19] Expression of *Trk-C* and shortened forms of *Trk-B* also portend a better outcome.[19] Together, these observations have led to speculation that functioning, intact Trk neurotrophin receptor pathways in these tumors may be linked further to the tumors' propensity to mature (differentiate) into ganglioneuromas or regress through a cell-death pathway (from a presumed eventual unavailability of factor for the receptor or from receptor malfunction). As knowledge of the role of these pathways had evolved, however, it has become clear that these receptors have potential as powerful markers of disease, or even as molecular therapeutic targets to manipulate neuroblastomas to assume differentiation or regression pathways.

Neuroblastoma may be stratified into specific prognostic subgroups based on the genetic interplay represented by *MYCN* expression, loss of heterozygosity, DNA ploidy, and neurotrophin-receptor expression. Combining these factors with age and stage, three genetic neuroblastoma profiles can be determined with differing survival rates (Table 53-2).

Table 53-2 Genetic Neuroblastoma Profiles

Feature	Type 1	Type 2	Type 3
MYCN amplification	None	None	Present
DNA ploidy	Hyperdiploid	Near-diploid	Near-tetraploid
Loss of heterozygosity	Rare	25-50%	Present
Neurotrophin gene expression	High	Low or absent (except Trk-B-high)	Low or absent (except Trk-B-high)
Age	1 yr	>1 yr	>1 yr
Stage	I, II, IVS	III, IV	III, IV
3-yr survival	95%	25-50%	<5%

Trk-B, tyrosine kinase receptor B.

Adapted from Brodeur G. Clinical and biological aspects of neuroblastoma. In: Vogelstein B, Kinzler KW, eds. *The Genetic Basis of Human Cancer.* New York: McGraw-Hill; 1998. With permission of The McGraw-Hill Companies.

DIAGNOSIS, STAGING, AND TREATMENT

The ultimate confirmation of the diagnosis of adrenal tumors is histologic electron microscopic tissue examination. Most tumors secrete catecholamines synthesized from the amino acid tyrosine in the sequence levodopa, dopamine (both excreted as homovanillic acid), and norepinephrine. In contrast to pheochromocytomas, neuroblastomas lack the ability to convert norepinephrine to epinephrine. Norepinephrine and epinephrine are excreted as vanillylmandelic acid. Urinary and serum levels of these secretory products form the basis of the prebiopsy evaluation of abdominal masses in children.

Imaging Techniques

The diagnostic algorithm in the imaging evaluation of abdominal masses in children has changed considerably since the early 1990s with the advent and availability of ultrasonography. An abdominal examination by ultrasonography detects most adrenal tumors. The term *incidentaloma* has been applied to tumors that are detected in the adrenal gland as an incidental finding in the course of pursuing an otherwise unrelated symptom, and this has become a more common way in which these tumors are found.[21] Two examples of such a presentation are shown in Figure 53-1. This tumor was discovered during the course of investigation of antenatally detected hydronephrosis, and a careful examination of the same area in previous ultrasound examinations confirmed the absence of the tumor previously.

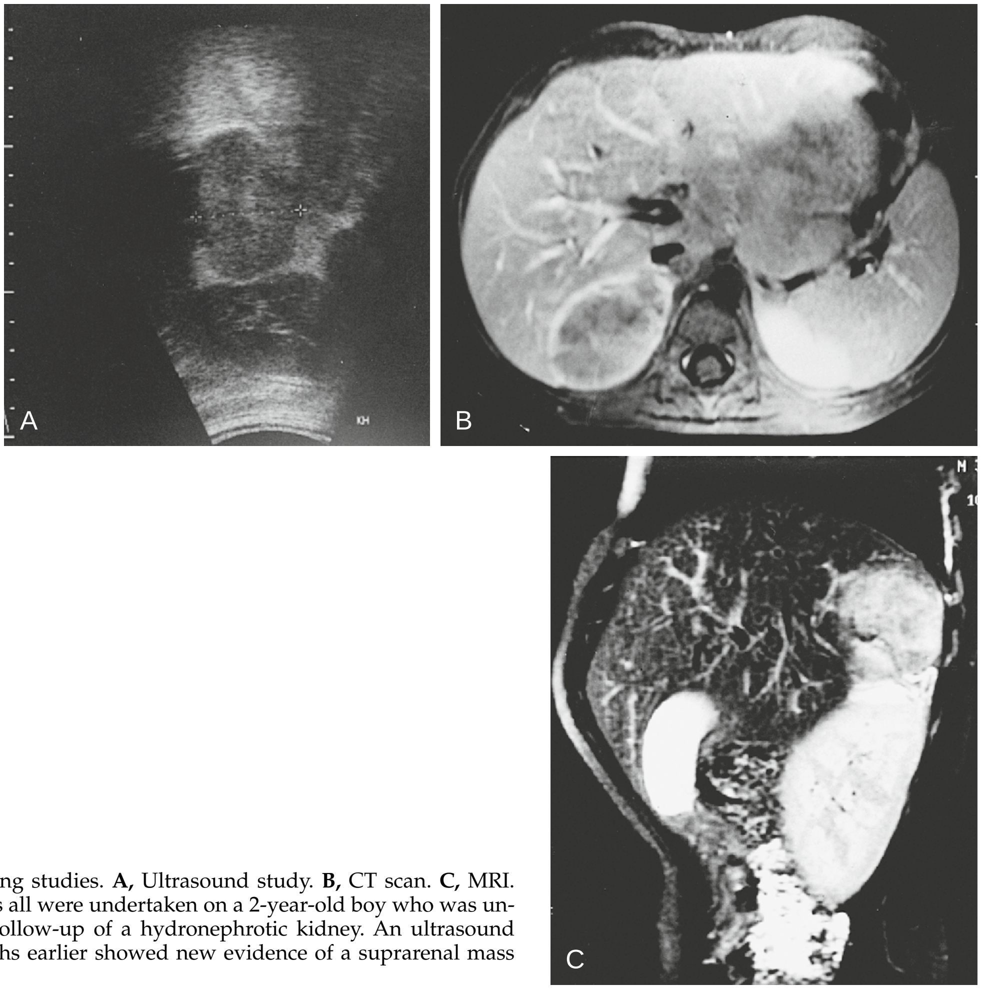

Figure 53-1 Imaging studies. **A,** Ultrasound study. **B,** CT scan. **C,** MRI. These investigations all were undertaken on a 2-year-old boy who was undergoing ongoing follow-up of a hydronephrotic kidney. An ultrasound study taken 3 months earlier showed new evidence of a suprarenal mass (not shown).

The diagnostic imaging techniques are evolving and improving with great rapidity, and there is no consensus about which technique—ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI)—is best. The time required for CT and MRI, along with the need for sedation in many cases, necessitates careful consideration in the selection of these studies in young children. Each of these techniques may be used to delineate and define the extent of disease, but the availability of the technique is the most critical determinant of which should be used. At the present time, CT seems to be the most widely available modality (Fig. 53-2; see also Fig. 53-1), although MRI is becoming more readily available in major centers. In seeking metastatic disease, a chest radiograph is a useful initial step, followed by radionuclear bone scanning with technetium 99m methylene diphosphonate, which is more accurate than a skeletal survey in the detection of bony metastases.

Prognostic Markers

The patient's age and tumor stage represent the most accurate predictors of the clinical outcome. Patients diagnosed at 1 year of age seem to show consistently better survival outcomes, even in the presence of advanced disease at presentation. Survival is dramatically related to the tumor stage at diagnosis, with 75% to 90% 5-year survival for stage I, II, and IVS patients compared with 10% to 30% 2-year survival for stage III and IV patients.

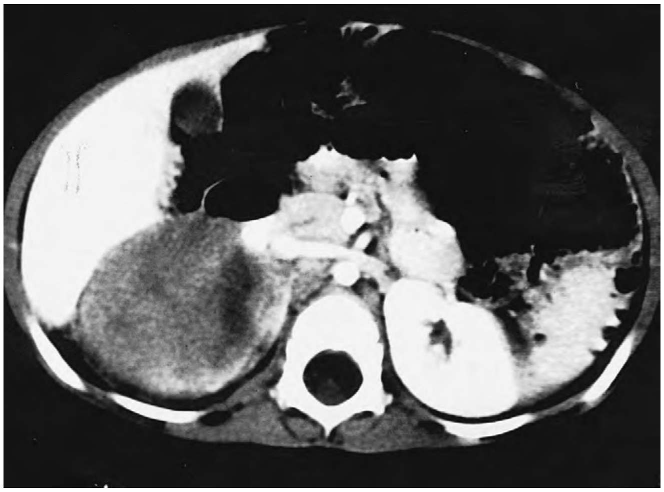

Figure 53-2 CT scan of a 4-year-old boy who presented with anemia and pain and showed this suprarenal mass, proved to be a neuroblastoma, with bony metastases.

Other measures related to biochemical or cell-related features are used in the diagnostic and prognostic evaluation of children. Serum ferritin levels may be elevated during periods of rapid tumor growth or large tumor burden or both. Ferritin levels seem to discriminate stage IV and IVS disease.[22] The lactate dehydrogenase level is a nonspecific measurement that may reflect rapid tumor cell turnover and tumor burden.[23] Neuron-specific enolase is a cytoplasmic enzyme found in cells of neural origin.[24] Neuroblastoma prognosis seems worse if elevated levels are detected in serum, although this marker is not specific to neuroblastoma.[24] Serum and tissue ganglioside G_{D2} is a glycosphingolipid shed by neuroblastoma tumor cells. It may reflect the tumor burden, and decreasing levels may be seen as a positive response to successful reduction of the tumor load. The presence of G_{D2} on the cell surface has attracted interest in targeting this molecule using immunotherapy strategies.[25-27] Finally, matrix metalloproteinases are cellular enzymes required to break down extracellular matrix and facilitate cell movement through the matrix during the metastatic process. In 1999, tumor cell expression of a membrane-associated matrix metalloproteinase was found to correlate with an advanced stage and poor outcome in neuroblastoma.[23]

Staging

A disease with such diverse manifestations as neuroblastoma in childhood needs a comprehensive staging system to allow (1) precise diagnostic criteria and (2) a method of categorizing and quantifying disease. An international working group published the outcome of its deliberations in 1988.[28] This staging system is known as the International Neuroblastoma Staging System (INSS), and the response criteria are referred to as the International Neuroblastoma Response Criteria (INRC). This staging system has replaced previous systems by Evans and coworkers,[29] originally established by the Pediatric Oncology Group (POG). Table 53-3 outlines the three staging systems for comparison.

Treatment

Therapy of neuroblastoma requires close coordination of medical, surgical, and radiation oncologists and represents a prime example of multimodal cancer therapy. Surgical intervention plays a dual role. At the time of diagnosis, open or laparoscopic approaches may be used to obtain adequate and thorough samples for histologic and molecular diagnosis and marker analysis. Needle biopsy materials are most often inadequate for these purposes. This approach also permits staging confirmation when the stage remains uncertain after tumor imaging is complete. For selected tumors, particularly small, locally confined ones, primary surgical excision may be possible. In this regard, laparoscopy may be considered and has been used successfully for small tumors identified by screening.[30]

Because the merits of screening seem lacking for the most aggressive, metastatic, and later presenting tumors, detecting instead tumors that may be the more biologically favorable to begin with, it may be reasonable to consider the laparoscopic approach as safe on oncologic grounds. Open surgical dissection is also employed to assess the response to therapy and excise residual disease after initial courses of chemotherapy have been completed. Two 1998 reports have suggested a higher incidence of nephrectomy in children with neuroblastoma who were treated with primary surgical intervention.[31,32] Two more recent reports of large series of patients confirm the benefits in prognosis of total resection of tumor, even in patients with local progression.[33,34] Based on the evidence in these reports, chemotherapy seems to provide little or no benefit in children in whom total surgical excision can be performed.

Although chemotherapy plays little role in the treatment of stage I and II tumors, it does seem to have a role in the treatment of higher stage disease. Single-agent and synergistic multiagent drug regimens are used that combine cell cycle–specific and cell cycle–independent drugs to achieve a maximal ratio of therapeutic benefit to toxicity. Multiple-agent regimens are many, varied, and ever-changing, and include combinations such as cyclophosphamide, doxorubicin, cisplatin, teniposide, and etoposide, which led to encouraging results of 40% survival in stage IV disease. Subsequent developments, based on these results, have led to more aggressive therapies, including myeloablative regimens, with bone marrow replacement. More recently, further, more aggressive therapy with marrow ablation, multiple monoclonal antibodies, and bone marrow transplantation have resulted in complete responses, or suitable shrinkage to allow surgical resection.[35] The use of autologous stem cell transplantation is being explored as an alternative to bone marrow transplantation in some centers.

Ionizing radiation has a role in neuroblastoma treatment because the tumor is radiosensitive. It is most useful in achieving local control and palliation of disease uncontrollable by other modalities. As a primary modality, however, radiotherapy is limited by the extensive metastatic proclivity of many neuroblastomas. The agent metaiodobenzylguanidine (MIBG), employed in the localization of neuroblastomas and pheochromocytomas, has been studied for its ability to bind neuroblastoma tumors systemically and carry with it radioligands such as iodine 131 that are toxic to the tumor cells.[25,36,37] This approach has also been used as an adjunct to guide surgical tumor tissue resection using the gamma camera intraoperatively after the tumor is radiolabeled by preoperative injection of iodine 131–labeled MIBG.[38]

Because of the aggressive nature of advanced and higher staged disease, efforts continue to improve disease control in this subset of patients, while refining therapy to limit toxicity in lower stage and more favorable disease.

Treatment

The ability to stratify patients into distinctly risk-related groups by application of the varied but highly accurate histologic and molecular diagnostic and staging methodologies has permitted a much more judicious and specific use of the therapeutic regimens. Stage I and II tumors (low risk) are treatable by primary surgical resection alone, with no need for initial chemotherapy or radiotherapy. A survival rate of 89% has been reported in this group of patients.[2,36,39] Stage IVS tumors undergo spontaneous remission and are considered low risk, but if symptoms related to severe hepatic metastatic disease or respiratory compromise are present, patients with these tumors may benefit from chemotherapy or radiation therapy in small doses.

Stage III patients (intermediate risk) still have an excellent overall survival rate of 89%,[39] but chemotherapy is advised after primary surgical excision. Second-look surgery may also be appropriate after chemotherapy. The goal of therapy in these children is to reserve more intense therapy and multiple courses of chemotherapy to children with biologically unfavorable tumors.

Stage IV patients (high risk) have derived minimal benefits from even the most intensive regimens. Multiagent chemotherapy remains the standard primary treatment strategy for these patients. The option of marrow ablative chemotherapy and bone marrow transplantation has been pursued in single institutions and resulted in some limited partial responses. These intensive therapeutic regimens are currently being explored in multicenter trials. The overall prognosis in these children remains poor (15% to 35% survival).[40]

Table 53-3 Neuroblastoma Staging System

Evans et al	POG	INSS
Stage I—tumor confined to organ or structure of origin	Stage A—complete gross resection of primary tumor, with or without microscopic residual. Intracavitary lymph nodes not adhered to and removed with primary tumor (nodes adhered to or with tumor resection may be positive for tumor without upstaging patient to stage C), histologically free of tumor. If primary tumor in abdomen or pelvis, liver histologically free of tumor	Stage I—localized tumor with complete gross excision without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with primary tumor may be positive)
Stage II—tumor extending in continuity beyond organ or structure of origin, but not crossing midline. Regional lymph nodes on ipsilateral side may be involved.	Stage B—grossly unresected primary tumor. Nodes and liver same as stage A	Stage IIA—localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically Stage IIB—localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
Stage III—tumor extending in continuity beyond midline. Regional lymph nodes may be involved bilaterally.	Stage C—complete or incomplete resection of primary tumor. Intracavitary nodes not adhered to primary tumor histologically positive for tumor. Liver as in stage A	Stage III—unresectable unilateral tumor infiltrating across midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
Stage IV—remote disease involving skeleton, bone marrow, soft tissue, and distant lymph node groups (see stage IVS)	Stage D—any dissemination of disease beyond intracavitary notes (i.e., extracavitary nodes, liver, skin, bone marrow, bone)	Stage IV—any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, or other organs (except as defined for stage IVS)
Stage IVS—patients who would otherwise be stage I or II, but who have remote disease confined to liver, skin, or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey)	Stage DS—infants <1 yr with stage IVS disease (see Evans et al)	Stage IVS—localized primary tumor as defined for stage I, 2IIA, or IIB with dissemination limited to skin, liver, or bone marrow (limited to infants <1 yr)

INSS, International Neuroblastoma Staging System; POG, Pediatric Oncology Group.
From Halperin EC, Constine LC, Tarbell NJ, et al. Neuroblastoma. In: *Pediatric Radiation Oncology*. 2nd ed. New York: Raven; 1994:182-183

PHEOCHROMOCYTOMA

Clinical Features and Presentation

Pheochromocytoma is an extraordinarily rare primary tumor of the pediatric adrenal medulla, although it is the most common hyperfunctioning form of this tissue. The tumors arise in the autonomic nervous system, and 90% originate in the adrenal gland. Catecholamine production is the norm and is the basis of the clinical manifestations and the most long-standing diagnostic method, which is based on measurement of circulating catecholamine levels. Over a 5-year period at The Hospital for Sick Children in Toronto, only 1 of 30 patients presenting with a primary adrenal tumor had a pheochromocytoma; this was a 16-year-old girl. In infants and young toddlers with ultrasound-diagnosed abdominal masses or hypertension, pheochromocytoma is extraordinarily rare. Pediatric pheochromocytomas can be seen in association with various diseases, including neurofibromatosis, von Hippel–Lindau disease, Sturge-Weber syndrome, and multiple endocrine neoplasia 2. Pheochromocytomas associated with multiple endocrine neoplasia 2 are more likely to occur later in life, and tumors that occur in association with these diseases are more likely to be bilateral.

Imaging, Biochemical Features, and New Prognostic Markers

The diagnosis of pheochromocytoma in childhood is suggested by the rare coexistence of hypertension and an abdominal mass detectable on ultrasound examination, although the latter may often be found in isolation. Nonpalpable pheochromocytoma causing secondary hypertension in children is exceedingly rare. The diagnosis is confirmed by means of either serum or urine detection of hypersecretion of catecholamines.

As stated previously, the principal catecholamine producing the characteristic symptoms of flushing, palpitations, hypertension (vasoconstriction), and anxiety in pheochromocytoma is epinephrine. Epinephrine is a metabolite of its precursor, norepinephrine. The latter is a less potent mediator of the clinical constellation seen in pheochromocytoma. Compared with neuroblastoma, however, both catecholamines are more likely to produce symptoms in pheochromocytoma than in neuroblastoma. Pheochromocytomas, particularly tumors of adrenal origin, produce the enzyme phenylethanolamine *N*-methyltransferase, which permits the conversion of norepinephrine to epinephrine. The norepinephrine-to-epinephrine ratio has been used to distinguish pheochromocytomas of adrenal origin from those of extra-adrenal origin.

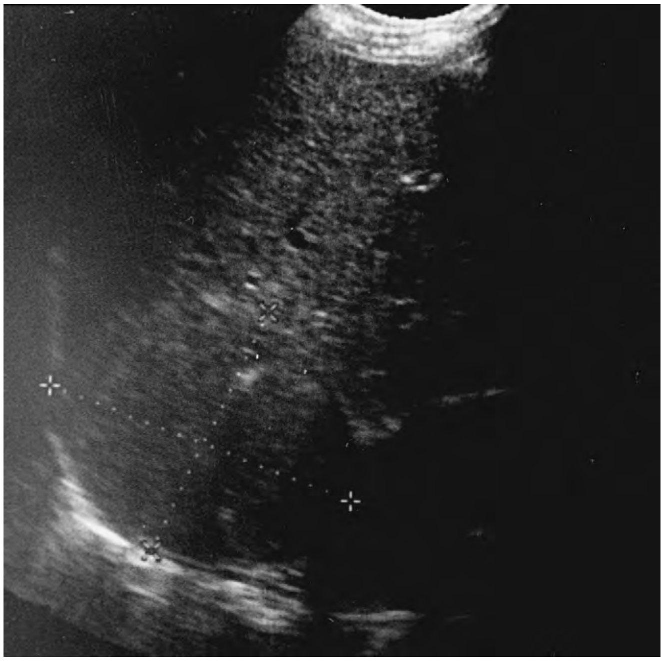

Figure 53-3 Ultrasound study of a suprarenal mass proved to be a pheochromocytoma in a 16-year-old girl who presented with headache and hypertension.

The initial diagnostic imaging modality in suspected cases is ultrasonography (Fig. 53-3). Either CT or MRI can be used to confirm the diagnosis of an adrenal or para-adrenal mass (Fig 53-4). Serologic or creatinine-specific measurements of catecholamine excretion in the urine are then undertaken. The most specific diagnostic imaging modality is radionuclide scanning using iodinated MIBG scintigraphy. With this approach, the sensitivity is greater than 90%.[41] Iodinated MIBG scanning is particularly valuable in the localization of tumors outside the adrenal gland.[42-44]

Differentiating benign from malignant pheochromocytoma is difficult. The occurrence of metastases has historically represented the only definitive feature of malignant disease. Newer markers for malignant pheochromocytoma include the nuclear enzyme telomerase[45,46] and an antibody specific for proliferating tumor cells, MIB-1. Although elevated telomerase activity is associated exclusively with malignant tumor cells, negative MIB-1 antibody labeling is reliably associated with benign pheochromocytoma.

Treatment

The historical importance of these tumors with respect to surgery is not the technical nature of their excision, but the cautions associated with the induction of anesthesia. These cautions are related to the potential for drastic changes in the excretion of catecholamines on manipulation and subsequent removal of the tumor. The challenges revolve around stabilization of blood pressure intraoperatively and the prevention of potential cardiovascular collapse at the time of tumor removal or ligation of the adrenal and associated veins delivering catecholamines to the systemic circulation. In infants, particularly in the preoperative state, these cautions are of great concern to parents, attending physicians, anesthesiologists, and surgeons. In view of the high specificity of contemporary serologic and radionuclide diagnostic methods, with current therapy these concerns may now be tempered.

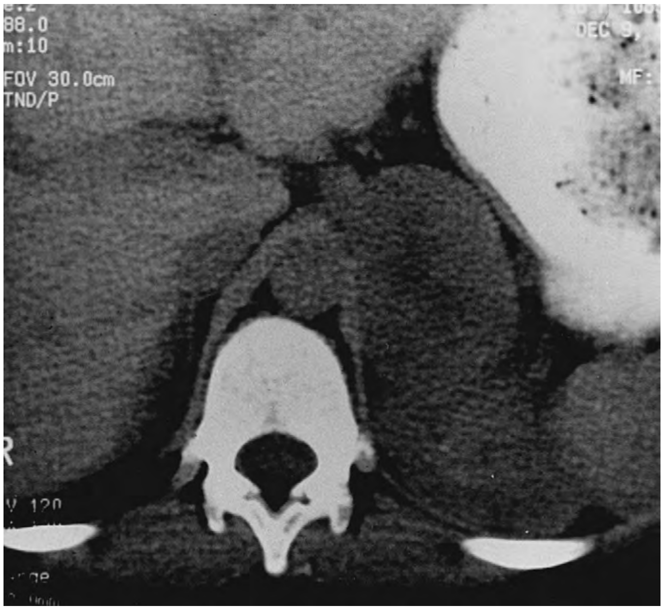

Figure 53-4 CT scan of the child shown in Figure 53-3.

As in adults, the mainstay of preoperative therapy includes blockade of α-adrenergic receptor function (phenoxybenzamine) accompanied by adequate systemic volume repletion. The use of cardiac β blockade (propranolol) in every case, to prevent reflex tachyarrhythmias, remains controversial, but should at least be considered in selected cases. Preoperative pharmacologic management of affected children should be undertaken in collaboration with the pediatric endocrinologist and anesthesiologist. If adequate blockade and volume repletion are achieved preoperatively, manipulation of the tumor is usually not accompanied by large variations in blood pressure, and large additional volume requirements are usually found unnecessary on tumor removal.

Open surgical incision by a flank or posterior lumbotomy approach may be considered. The newest data relate to laparoscopic removal. Rutherford and associates[47] published an excellent review of the laparoscopic experience with these tumors. They noted that the patients treated with a laparoscopic surgical approach to the adrenal gland have a significant reduction in recovery time and a low complication rate. The similarly beneficial results regarding laparoscopic removal may allow it to become the most widely accepted method of surgical excision.

ADRENAL CARCINOMA

Adrenal carcinoma represents less than 0.0001% of children's neoplastic tumors. The most common presentation is abnormal virilization, occurring in two thirds.[48] Cushing syndrome accounts for a further third. Individual case reports have reported occasional aldosterone-secreting tumors. Given the widespread availability of ultrasound imaging technology, the most common presentation may now be as an incidental finding on abdominal ultrasonography undertaken for vague or varied indicators. A multicenter registry has published its findings on the clinical and diagnostic characteristics in these rare tumors in childhood.[49]

Adrenocortical tumors may also be a component of more global genetic malformations; these include congenital adrenal hyperplasia or multiple endocrine syndromes (multiple endocrine neoplasia 1) and Beckwith-Wiedemann syndrome. A cohort of patients has been identified in Brazil with a specific genetic mutation that predisposes to adrenocortical tumors.[50]

Clinical Presentation

Virilizing Adrenal Tumors

Of the functioning adrenocortical tumors, virilizing forms account for two thirds and usually occur in children older than 2 years. The tumors produce dehydroepiandrosterone, a weak androgen but one that is converted to Δ^4-androstenedione and testosterone, which are more potent virilizing hormones. Boys with such tumors present with precocious puberty evidenced by excessive maturation of the genitalia. Girls develop an abnormal increase in clitoral size, similar to that seen with congenital adrenal hyperplasia. Pubic and axillary hair may be seen in children of both sexes.

Alternate causes of increased virilization in boys include sexual precocity or premature pubarche, interstitial cell tumors of the testis, and delayed manifestation of congenital adrenal hyperplasia. Clinical evaluation may give some clues to distinguish these cases. Examination of the scrotum gives some evidence of Leydig cell tumors by means of unilateral or asymmetric enlargement of the testes. With sexual precocity, testicular enlargement is bilateral. With virilizing adrenal tumors, the testes are usually small. The differential diagnosis in girls includes ovarian arrhenoblastoma and other rare tumors of the adrenal cortex.

Cushing Syndrome

Approximately one third of children with adrenocortical tumors may have stigmata of Cushing syndrome. Carcinoma may be responsible in half, with the others having evidence of bilateral adrenal hyperplasia. A benign adenoma may rarely be seen. The clinical presentation is related to excessive production of cortisol leading to protein catabolism, subsequent increased gluconeogenesis, and the typical obesity associated with cortisol excess. Moon facies, truncal obesity, and typical evidence of Cushing disease are generally obvious in infants.

The differential diagnosis in cases exhibiting excess adrenocortical activity includes adrenal adenomas and iatrogenic administration of steroids. This latter iatrogenic excess is commonly seen in children receiving transplanted organs.

Feminizing Adrenal Tumors

Feminizing adrenal tumors are rare. They are more commonly seen in boys, and in these cases the differential diagnosis with primary gynecomastia must be elicited.

Diagnostic Evaluation

In all these tumors, biochemical determination of adrenal hyperfunction leads to the exact nature of the hormone excess. Urinary steroid levels may be elevated, but serum levels of free cortisol and 17-hydroxysteroid are generally available and are abnormally elevated.

Provocative tests with corticotropin stimulation may aid in distinguishing primary adrenocortical adenomas from adenomas in which endogenous corticotropin levels are increased. Modern diagnostic imaging has given the greatest advances since the early 1990s. Incidentalomas are now commonly detected on ultrasonography. MRI in addition to ultrasound has led to tremendous advances in the ability to distinguish adrenal carcinoma from benign adenomas.[51,52]

Treatment

Treatment of adrenocortical carcinoma is surgical. The rate of development of new instrumentation, particularly in laparoscopic procedures makes any textbook summary of these techniques outdated by the time the text is published. In children, open surgical removal may be accomplished by large transverse abdominal incisions or, in some instances, by extended flank incisions. Laparoscopic removal is now widely employed in adult surgery, but the current lack of small instrumentation limits its use in very small children.[53] The advances in imaging allow more limited surgical approaches than may have been previously encountered. A tumor diameter of more than 5 cm is a reasonable predictor of malignancy, whereas small adenomas may be approached with more conservative surgery. Despite the advantages of modern imaging, the current data show a continued reliance on surgical excision as the mainstay of therapy.[54,55] Preoperative care must recognize the need for corticosteroid replacement in cases in which an excess of corticosteroids is anticipated.

The prognosis for adrenal carcinoma is poor. Surgery is the primary therapy, and chemotherapy has not been effective in controlling widespread disease.

REFERENCES

For complete list of references log onto www.expertconsult.com

PART IX

EMERGENCIES AND TRAUMA

CHAPTER 54

NEONATAL UROLOGIC EMERGENCIES

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Abnormalities discovered in the prenatal and perinatal period are often a cause of concern, anxiety, and apprehension on the part of the parents and physician. Some of these abnormalities are quite rare. Specific initial management measures are required to ensure the best possible results. This chapter reviews the most common neonatal urologic emergencies, their presentations, and initial management steps during the first 24 to 48 hours of neonatal life. Further management details, after the initial stabilization period, are discussed elsewhere in this text. The reader should refer to those specific topics as necessary.

URINE PRODUCTION

Oligohydramnios

After 16 weeks of gestation, the amniotic fluid begins to transition from a placental transudate to a reflection of actual fetal urine production. By 22 weeks, nearly all of the amniotic fluid is a product of fetal urine. Oligohydramnios represents either an inability to produce urine or an impaired ability to void. Typically, the more severe the oligohydramnios, the more ominous the underlying pathology. In its most extreme form (Potter syndrome, renal agenesis), oligohydramnios is associated with limb contractures, low-set ears, and compressed facies. Absent renal function is seen in bilateral renal agenesis, bilateral multicystic renal dysplasia, or juvenile polycystic kidneys. These infants rarely survive beyond the first few hours. No specific therapy is available, and the role of the urologist is to provide counseling (Fig. 54-1). Otherwise, oligohydramnios represents the inability to void because of obstruction in the urinary tract.

Delayed Voiding

One of the most common urologic concerns of the newborn period is the absence of voiding. Most commonly, this represents delayed voiding. It is imperative to recognize that a normal neonate may not void for 24 hours or more.[1] In the face of a normal amount of amniotic fluid, one can be reasonably assured that the fetus has been able to void throughout fetal life. The most informative finding on physical examination is the presence of a distended bladder. The examination itself may precipitate voiding. If voiding does not occur within 24 hours, or with a particularly distended bladder, an abdominal ultrasound scan is warranted. If there has been oligohydramnios or bilateral prenatal hydronephrosis, an immediate investigation beginning with a renal and bladder ultrasound followed by a voiding cystourethrogram (VCUG) is required. Specific pathologic findings are discussed subsequently.

Hematuria

Gross hematuria in a newborn, although uncommon, is a urologic emergency. Although no specific abnormality may be found, life-threatening conditions, such as renal vein thrombosis and renal artery thrombosis, may be the cause (see later). Immediate evaluation and appropriate treatment is mandatory. Other causes include renal calculi, infections, ureteropelvic junction obstructions, and other anomalies. One theory is that urethral bleeding can result from a withdrawal of maternal hormones.[2] The evaluation should consist of a physical examination including blood pressure, urine culture, renal ultrasound, and complete blood count with platelet count. Further workup is guided by these initial studies.

GENITAL CONDITIONS

Hypospadias

Hypospadias is a common urologic abnormality discovered in neonates. An inability to identify the location of the meatus often leads to a urologic consultation. Obstruction is almost never present, and gentle probing with a 5F feeding tube (although unnecessary) proves patency. Hypospadias does not represent an emergent condition, and no immediate intervention is required. The more proximal the hypospadias, the more common the presence of chordee and foreskin with a characteristic dorsal hood appearance. A distal hypospadias may be discovered at the time of circumcision; if so, the procedure should be aborted immediately in an attempt to salvage foreskin that may be used for later corrective surgery. If an incision has been performed, it should be repaired. Circumcision should not be performed until the time of corrective surgery later in life. The combination of hypospadias (especially a more proximal hypospadias) and a nonpalpable testicle is suspicious for an intersex condition and should prompt an appropriate workup.

Circumcision Complications

The most common complication after circumcision is bleeding. Many of these bleeding episodes can be managed with the application of gentle pressure. An epinephrine-soaked gauze may help. If persistent, placement of interrupted dissolvable sutures may be required for homeostasis. Particularly troublesome bleeding should raise the suspicion for an underlying

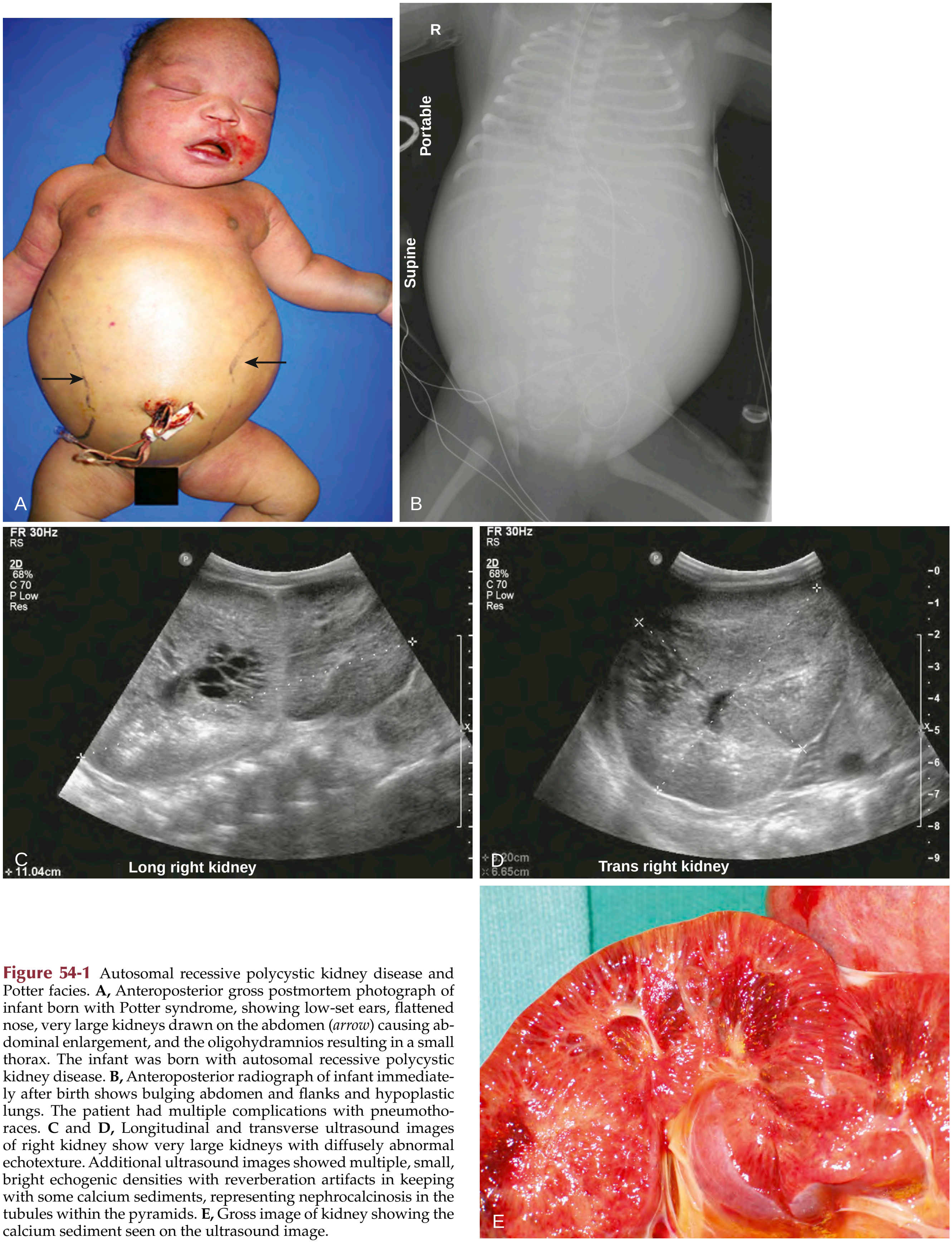
A
R
Portable
Supine
B
FR 30Hz
RS
2D
68%
C 70
P Low
Res
C
11.04cm
Long right kidney
FR 30Hz
RS
2D
68%
C 70
P Low
Res
-0
-1
-2
-3
-4
-5
-6
-7
-8
-9
D
20cm
6.65cm
Trans right kidney
E

Figure 54-1 Autosomal recessive polycystic kidney disease and Potter facies. **A,** Anteroposterior gross postmortem photograph of infant born with Potter syndrome, showing low-set ears, flattened nose, very large kidneys drawn on the abdomen (*arrow*) causing abdominal enlargement, and the oligohydramnios resulting in a small thorax. The infant was born with autosomal recessive polycystic kidney disease. **B,** Anteroposterior radiograph of infant immediately after birth shows bulging abdomen and flanks and hypoplastic lungs. The patient had multiple complications with pneumothoraces. **C** and **D,** Longitudinal and transverse ultrasound images of right kidney show very large kidneys with diffusely abnormal echotexture. Additional ultrasound images showed multiple, small, bright echogenic densities with reverberation artifacts in keeping with some calcium sediments, representing nephrocalcinosis in the tubules within the pyramids. **E,** Gross image of kidney showing the calcium sediment seen on the ultrasound image.

bleeding diathesis, and an evaluation should be performed. Minor injuries to the glans or shaft should undergo primary repair. Careful inspection for urethral involvement must be performed when evaluating a circumcision injury. In the event of urethral involvement, the authors prefer a conservative initial approach with plans for delayed repair and catheter drainage only if necessary.

Enlarged Scrotum

Newborns presenting with an enlarged scrotum need immediate evaluation. Differential diagnosis includes hydrocele with or without hernia, epididymitis, orchitis, testicular torsion, hemorrhagic infarction, torsion of the testicular appendix, and neoplasm.

Hydroceles and Hernias

Hydroceles and hernias are characterized by a transilluminating scrotum with a fluid-filled consistency, often with a slightly bluish hue. If compression of the fluid shows communication with the abdomen, the processus vaginalis is patent, and there may be an associated hernia. These carry the risk of future incarceration of bowel and must be followed closely, with surgical correction on an elective basis. Noncommunicating hydroceles are generally nontender. Most resolve spontaneously within the first year of life. If persistent or progressive, they may be corrected on an elective basis (Figs. 54-2 and 54-3).

Perinatal Testicular Torsion

Perinatal testicular torsion refers to prenatal torsion (torsion occurring before birth) and postnatal torsion (torsion occurring shortly after birth). Both conditions usually manifest as an enlarged, often hardened hemiscrotum. The skin may be bluish to varying shades of red, and often has associated ecchymosis and erythema. The testicle may be slightly higher in the scrotum than the contralateral side and can be difficult to palpate depending on the amount of edema present. Most prenatal torsions are nontender, whereas early recognized postnatal torsion may still be tender on palpation. Although the physical examination may be suggestive of the diagnosis, if available a confirmatory emergent scrotal ultrasound scan is required. In the event of a testicular torsion, scrotal

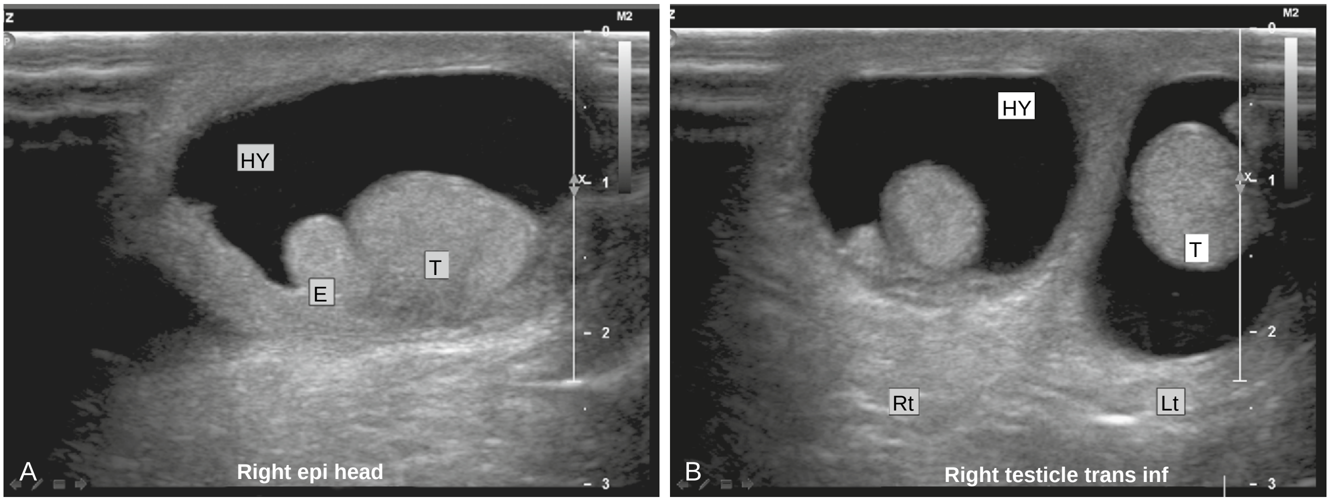

Figure 54-2 Bilateral hydroceles. **A,** Longitudinal ultrasound of right testicle (T) and head of the epididymis (E). HY, hydroceles. **B,** Transverse ultrasound of scrotum (the right [Rt] and left [Lt] hemiscrotum) show bilateral anechoic hydroceles (HY) with normal testicles (T) and epididymis.

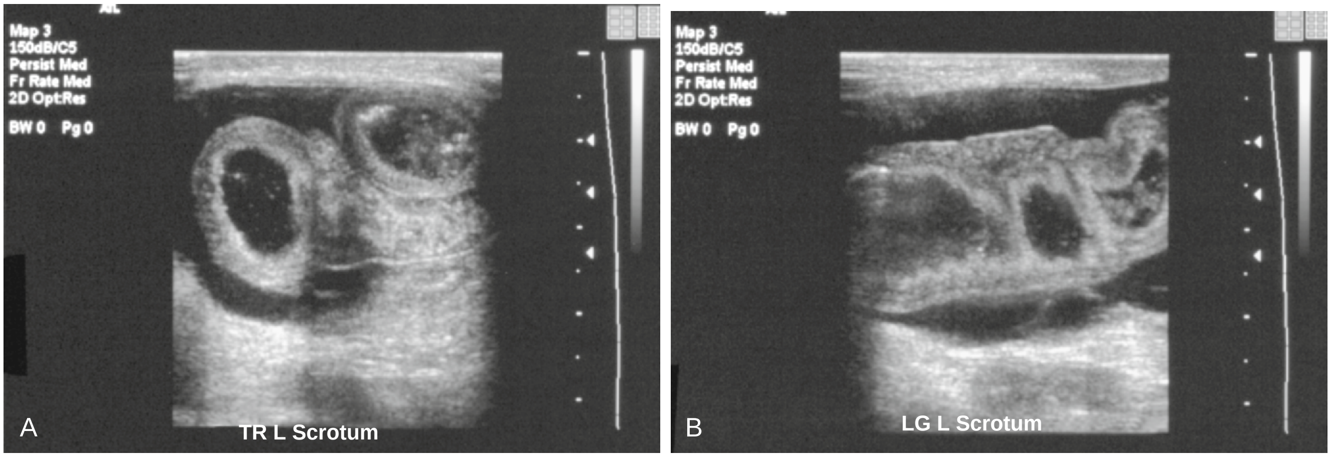

Figure 54-3 Incarcerated inguinal hernia. **A** and **B,** Transverse and longitudinal images of left scrotum show bilateral anechoic hydroceles with presumed patent processus vaginalis, and herniated loop of small bowel, which is also thickened.

ultrasound reveals a heterogeneous, hypoechoic testicle with a brightly echogenic rim. Additional findings may include areas of necrosis, subtunical fluid, or hydrocele.[3] Although the specificity and sensitivity of ultrasound in the detection of torsion vary in the literature, color and enhanced power Doppler imaging have improved the sensitivity (Fig. 54-4).[4,5]

As in all cases of testicular torsion, prompt diagnosis is the key. Most prenatal torsions are recognized beyond a time frame for salvage. This is not to be confused with postnatal torsion or torsion that occurs after a normal physical examination has been performed. Such postexamination torsion requires immediate intervention as would be done for any later torsion—surgical detorsion and orchidopexy are required in an attempt to salvage the testicle.[6] Also, if there is any doubt as to the timing of the presentation, or if there is uncertainty about the initial examination, postnatal torsion must be assumed, and surgery must be performed.

For prenatal torsion, there is much debate about surgical intervention. Although salvage rates of 50% have been reported,[7] it is generally believed to be quite poor, with one large series reporting 0%[8] for prenatal torsion and another reporting 5% for prenatal and postnatal combined.[9] Immediate surgery provides the opportunity for contralateral orchidopexy. This is also controversial, but generally adds minimal morbidity. Because the likelihood of salvage is near zero for true prenatal torsion, the anesthetic risks during the first 30 days of life may outweigh the low incidence of asynchronous contralateral torsion. Although none of the reported series report anesthetic complications, most of these were at pediatric hospitals with neonatal anesthesiologists.[3,7]

Proponents of immediate surgery worry that although the incidence of asynchronous contralateral torsion is low, asynchronous contralateral torsion has been reported and carries the outcome of anorchia. Some support careful observation with serial scrotal examinations by the parents, whereas critics point out that the subtle signs of early torsion may not be apparent to the layman. Additionally, the examination is more complex in the presence of a hydrocele. Bilateral synchronous torsion, although uncommon, has been reported.[9] If there is any concern for bilateral involvement, immediate surgical exploration is warranted. These decisions should occur with well-informed parents and take into consideration multiple factors. Availability of pediatric anesthesia, stability of the patient, proximity to neonatal health care for the family, presence of hydrocele that may make examination more difficult, and family reliability all should be weighed in this process.

Neonatal Testicular Tumors

Although rare, neonatal testicular tumors have been reported, including teratoma and paratesticular neuroblastoma. In many cases, these tumors have manifested as perinatal testicular torsions.[10,11] If tumor is suspected, an inguinal approach with biopsy is recommended.

Ambiguous Genitalia

Newborns with ambiguous genitalia represent true urologic emergencies and represent some of the most challenging clinical cases for the physician and family. Parents are faced with uncertainty, confusion, and anxiety, and require education and counseling often for an extended period. These children need immediate medical evaluation to rule out a life-threatening condition. This evaluation should always be a team approach and include a neonatologist, pediatric endocrinologist, geneticist, pediatric urologist/surgeon, and the parents. The external genitalia present a wide spectrum of abnormalities. The evaluation should be thorough and include a detailed history, including a list of medications taken during pregnancy, family history of stillbirths, unexplained neonatal deaths, or intersex conditions. A careful physical examination must emphasize all phallic characteristics, including the position of the urethral meatus, labial/scrotal development and pigmentation, and the presence of palpable gonads in the labioscrotal folds or in the inguinal canals. Initial laboratory studies include a basic metabolic panel and a karyotype.

This initial evaluation is an emergency to detect and treat neonates with salt-wasting seen in congenital adrenal hyperplasia (CAH) with 21-hydroxylase deficiency. Genetic female neonates with phenotypic virilization may have CAH, a pathologic

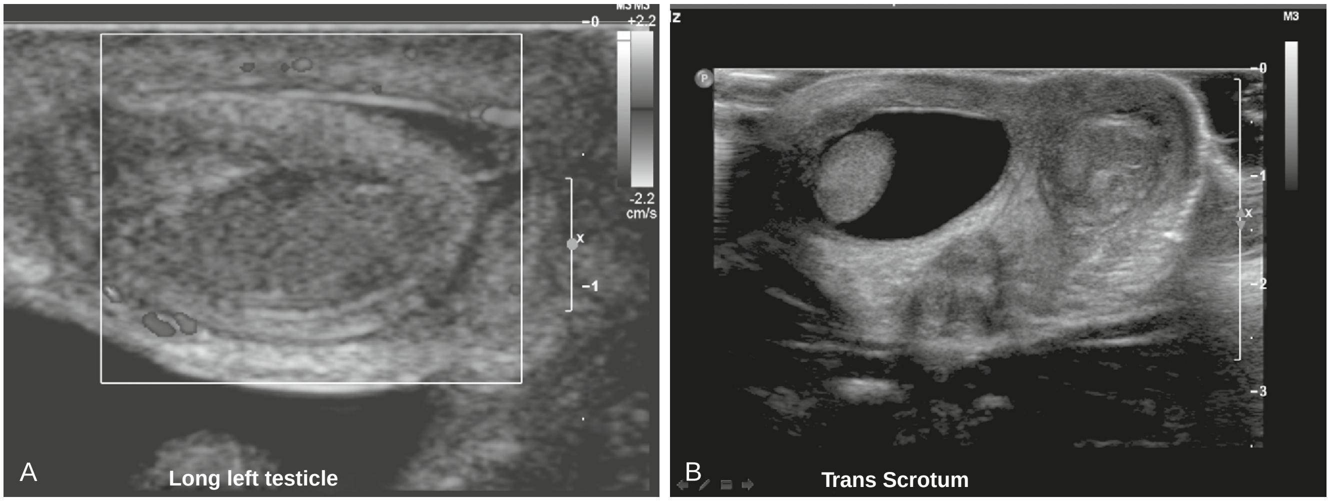

Figure 54-4 Left testicular torsion. **A,** Longitudinal ultrasound of left testicle with color Doppler shows abnormal echogenicity of the left testicle and thickening of the periphery with small hydroceles. On color Doppler, no blood flow was shown. This appearance is in keeping with testicular torsion. **B,** Transverse image of scrotum showing both testicles. The left testicle is enlarged, showing abnormal mixed echotexture with edema of the left hemiscrotum. The appearance with mixed echotexture is compatible with torsion. The normal homogeneous right testicle is shown and is surrounded by an incidental hydrocele.

condition that is potentially deadly, but treatable. CAH includes a spectrum of enzymatic deficiencies, some of which are not life-threatening, but also cause phenotypic virilization in genetic females. About 95% of children presenting with CAH have 21-hydroxylase deficiency. CAH results in inadequate synthesis of cortisol and subsequent overproduction of androstenedione and 17β-hydroxyprogesterone. The severity of the genotype varies resulting in the phenotypic variations.

If the impairment of aldosterone/cortisol production is severe enough, with the 21-hydroxylase form of CAH, the child may present as a "salt-waster" and develop an adrenal crisis characterized by life-threatening hyponatremia, hyperkalemia, and hypovolemic shock. Usually these infants present within several days of birth with nonspecific symptoms, such as poor appetite, vomiting, lethargy, and failure to gain weight.[12] Simple virilizers (i.e., "non–salt-wasters") have enough aldosterone production to avoid an adrenal crisis, but still show phenotypic virilization. Early recognition is paramount to prevent lethal consequences. When a definitive gonad can be palpated in a neonate with genital ambiguity, it is usually a testicle, greatly reducing the likelihood of CAH.

Treatment for salt-wasters includes correction of hypovolemia and administration of hydrocortisone (usually 10-15 mg/m^2/day orally divided twice to three times per day and fludrocortisone, an aldosterone analog 0.1 mg per day. Although controversial, prenatal treatment with dexamethasone for high-risk pregnancies (pregnant women with prior history of affected offspring) has been used.[12] New[13] has shown excellent results in minimizing the virilizing effects in treated fetuses, apparently with no identifiable morbidity. The long-term effects of this therapy on affected and unaffected children are unclear, however.

CAH is the most common of several conditions that can lead to disorders of sexual differentiation. Whatever the cause of ambiguous genitalia, one of the most controversial and most challenging aspects of the care of these children is in the decision of sex of rearing. These decisions should always be made with contributions from the entire gender assignment medical committee in conjunction with the parents. There are several factors to consider when discussing this issue with the parents, many of which will not be determined in the first few days. It is important not to make any assumptions during this period and to explain this clearly to the parents and ancillary staff. Gender-neutral terminology should be used. The parents should be discouraged from assigning a name to the child until all information is obtained. In cases of ambiguity secondary to structural abnormalities (as in cloacal anomalies), gender assignment is unnecessary, but chromosomal analysis may be required for proper sex determination.

Intralabial Masses

A perineal mass in a newborn girl should prompt an immediate examination. Appearance alone is suggestive of the diagnosis in most instances; however, an ultrasound scan of the vagina and bladder is important. Periurethral cysts are the most common and are derived from the periurethral glands. They are whitish in appearance, are covered with normal-appearing epithelium, and are located in the anterior vaginal wall, inferolateral to the meatus.[14] No emergent intervention is required; however, incision is curative. Hydrocolpos from an imperforate hymen manifests as a midline bulging mass at the posterior introitus. The mucosa is slightly transparent and appears pearly white. A palpable suprapubic mass may be present. An ultrasound scan confirms the distended fluid-filled vagina and location of the bladder. Incision and drainage is curative.

Vaginal rhabdomyosarcoma (botryoid sarcoma) commonly manifests with vaginal bleeding and has a distinctive appearance of a cluster of grayish masses (bunch of grapes) prolapsing through the introitus.[14] Although no immediate surgical intervention is necessary, prompt evaluation in conjunction with the pediatric oncology team is mandatory. A prolapsing ectopic ureterocele may manifest as a mass protruding from the urethra. Covered with bladder epithelium, these masses often appear dark in color, bluish or purple, and edematous or even necrotic. Ureteroceles protruding from the urethra may result in bladder outlet obstruction, and a palpable bladder may be identified. The prolapsed ureterocele sometimes can be reduced. A Foley catheter should be placed to drain the bladder temporarily and prevent repeat prolapse until the ureterocele can be incised (see section on ureteroceles).

BLADDER

Megacystis

Prenatal detection of an enlarged bladder should prompt close follow-up. Nonobstructive causes of bladder distention are usually associated with a thin-walled bladder and normal amniotic fluid levels, whereas obstructive causes typically have a thickened bladder wall and associated oligohydramnios. There is a varied spectrum between these presentations, however. It is difficult to categorize because of the variability with bladder fullness at time of the ultrasound scan. Complete bladder outlet obstruction resulting in megacystis associated with severe oligohydramnios is often incompatible with life, with pulmonary complications causing most of the immediate concerns.

The differential diagnosis mainly consists of posterior urethral valves (PUV), anterior urethral valves, prune-belly syndrome, urethral atresia, and bladder neck obstruction from an ectopic ureterocele. These conditions represent a true emergency in which immediate bladder drainage is required (although not necessarily true for prune-belly syndrome; see later section). An ultrasound scan and VCUG should assist with the diagnosis and must be performed within the first 24 to 48 hours of life. As previously stated, complete obstruction of urine has a poor prognosis. Often these obstructions are diagnosed prenatally, and fetal interventions with the placement of a vesicoamniotic shunt or periodic vesicocentesis with amnioinfusions have been performed.

Umbilical Drainage

Umbilical drainage may be a presenting sign for various conditions. The physical examination should help determine if urgent intervention is required. The umbilicus may be swollen and erythematous with or without purulent drainage, and a midline abdominal mass may be identified. More often, asymptomatic serous drainage is discovered. The neonate may present with local or systemic infection. The differential diagnosis includes an infected umbilical stump, persistent urachal sinus, urachal cyst, urachal diverticulum, patent urachus, and a patent omphalomesenteric duct. Abdominal ultrasonography is usually sufficient to characterize the extent of the tract and to rule out cystic fluid collections. A VCUG is obtained to rule out a persistent urachus, defined by a communication with the bladder. Injection of the umbilicus with contrast fluid under fluoroscopy may aid in the diagnosis; however, this is often difficult to perform.

Many of these conditions can be managed conservatively. The primary concern in the neonatal period is the presence or absence of an infection. Antibiotic therapy is usually sufficient for local infections and should be the first-line therapy.

If systemic infection is present, intravenous antibiotics are mandatory. Cystic fluid collections, especially if particularly large, may need to be drained either surgically or percutaneously in the setting of systemic infection.

Bladder Exstrophy

The diagnosis of bladder exstrophy is usually apparent at birth and may be suggested on prenatal imaging by an inability to identify the bladder on multiple prenatal ultrasound scans. The physical examination should pay particular attention to the size and appearance of the bladder template. Although these children are usually born at term and are otherwise healthy, a renal ultrasound scan should be obtained to rule out any associated renal pathology. Immediate management centers on the protection of the exposed bladder epithelium. The umbilical cord is tied off with a 2.0 silk suture away from the bladder.[15] Clear plastic (usually Saran Wrap) is used to drape the exposed bladder epithelium. This should be changed and the mucosa irrigated with normal saline at all diaper changes.[15] Adhesive or adherent dressings should be avoided. Creating a plan for bladder closure is the next step. The technique of closure is debated. The most important aspect of surgical management is the use of a specialized exstrophy center with surgeons who are particularly experienced with this condition and have the appropriate resources.

UPPER TRACT

Hydronephrosis

The most common urologic abnormality identified in the prenatal period is the presence of hydronephrosis. Hydronephrosis may be an isolated finding or be associated with various urologic abnormalities. Following some general principles, one can readily identify potential emergencies from more elective evaluations. As previously mentioned, the history of any oligohydramnios is of paramount importance. In the case of a normal amount of amniotic fluid throughout pregnancy, one can be assured that the fetus has been able to urinate. The urologist must inquire about any family history of hydronephrosis or other urologic pathology, especially in previous pregnancies. Characterizing the hydronephrosis as unilateral versus bilateral and noting any ureteral involvement or distended bladder narrow the differential diagnosis (Table 54-1). Viewing the prenatal ultrasound scan is helpful, but the scan is often unavailable.

The infant should be placed on prophylactic antibiotics immediately until vesicoureteral reflux (VUR) has been ruled out. For otherwise healthy newborns, amoxicillin, 10 mg/kg/day, is sufficient. An ultrasound scan after birth is required to define the hydronephrosis and note any changes from prenatal reports. Timing of the renal ultrasound scan has been debated. In the first 24 hours of life, there is a relative oliguria of the newborn, and this may underestimate the amount of hydronephrosis present or potentially lead to false-negatives. Many clinicians wait 48 hours or longer to perform the ultrasound. Docimo and Silver[16] reported no abnormalities discovered in 101 patients, however, after a normal ultrasound done within 48 hours. In the presence of severe hydronephrosis or any bilateral hydronephrosis in a boy, or if there are other accompanying urologic anomalies, the authors prefer to perform the ultrasound scan within 24 hours.

Independent of hydronephrosis grade, a VCUG should generally be obtained to rule out VUR. Thirty percent of prenatally diagnosed cases of hydronephrosis have VUR.[17] The urgency with which the VCUG is obtained varies depending on hydronephrosis present. Grades I through III unilateral hydronephrosis do not represent an emergency, and the VCUG may be done as an outpatient procedure usually within 1 month. If there is any question of family reliability, the VCUG should be done before they leave the hospital. If there is a history of oligohydramnios, outlet obstruction must be ruled out even with unilateral hydronephrosis, and the VCUG should be done without delay. Prophylactic antibiotics may be discontinued in the absence of VUR.

Generally, processes that do not affect either both kidneys or a solitary kidney are rarely true emergencies. When at least one normal-appearing kidney is identified, and there is no history of oligohydramnios, emergent intervention is usually not required. A bilateral process or one that affects a solitary functioning kidney can have a profound effect, however, on overall renal function even with less severe-appearing presentations. Oligohydramnios is a good predictor that significant pathology exists despite mild imaging abnormalities.

Ureteropelvic Junction Obstruction

Unilateral ureteropelvic junction obstruction usually does not represent a urologic emergency. If the kidney has the appearance of functional parenchyma on imaging, complete obstruction is unlikely. Nuclear renal scan performed after 2 to 4 weeks and serial ultrasound scans ultimately confirm the diagnosis and reveal any functional impairment. Even if the child has severe renal impairment, most urologists would defer repair until anesthetic risks have decreased (4 to 6 weeks of age). In the case of bilateral ureteropelvic junction obstructions in which there seems to be an effect on renal function, such as a history of oligohydramnios, early intervention may be required. This usually involves bilateral percutaneous nephrostomy tube placement (Fig. 54-5).

Table 54-1 **Differential for Hydronephrosis**

Presentation	Most Common	Common Causes	Rare Causes
Unilateral hydronephrosis	UPJ	MCDK, VUR, duplication	External compression from abdominal mass
Bilateral hydronephrosis	VUR	Bilateral UPJ; combination of MCDK, VUR, or duplication	PBS, PUV
Unilateral hydroureteronephrosis	VUR	Ureterocele, duplication, megaureter, ectopic ureter	External compression from abdominal mass
Bilateral hydroureteronephrosis	PUV	Bilateral megaureters, bilateral duplication, bilateral ureteroceles, PBS	Urethral atresia

MCDK, multicystic dysplastic kidney; PBS, prune-belly syndrome; PUV, posterior urethral valves; UPJ, ureteropelvic junction obstruction; VUR, vesicoureteral reflux.

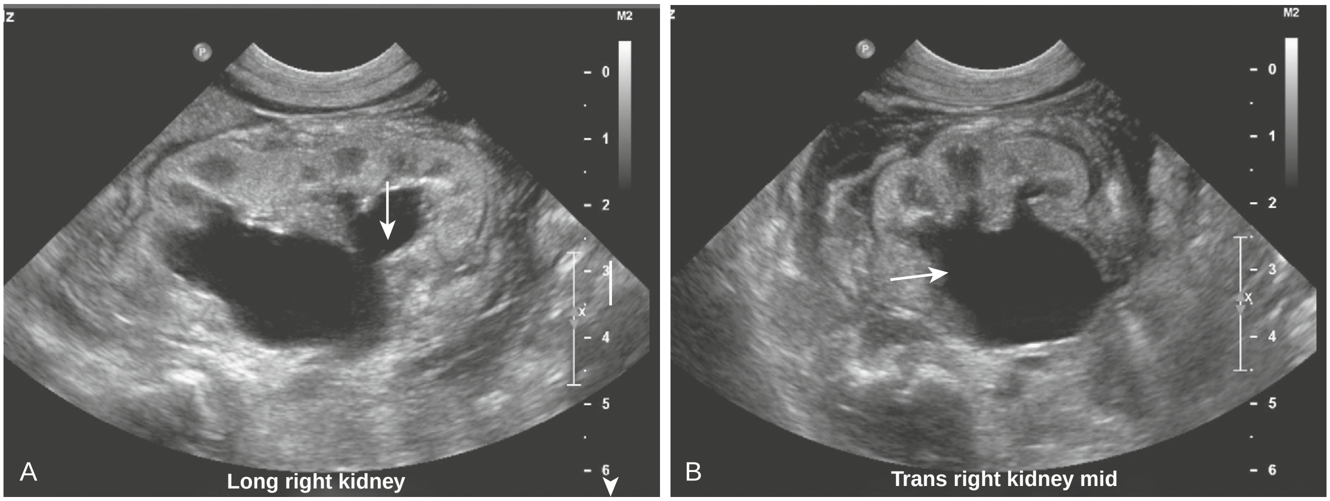

Figure 54-5 Ureteropelvic junction obstruction. **A** and **B,** Longitudinal and transverse images of the right kidney in a 5-day-old infant showed early grade 4 hydronephrosis with anechoic (*arrow* in **A**) urine in the dilated collecting system. Note the hypoechoic pyramids, which are often mistaken as dilated calyces; in this case the distinction is visible. The transverse image shows the large and dilated renal pelvis (*arrow* in **B**) as well; the ureter was not visible (not shown here).

Ureteroceles

Prenatal ultrasonography has led to an increase in the diagnosis of ureteroceles, most of which are associated with duplicated systems in girls and solitary systems in boys.[18] Most do not require immediate surgical management, but should be evaluated promptly. If a child has an antenatal history of a ureterocele, a confirmatory renal/bladder ultrasound scan and VCUG need to be obtained. Various degrees of hydronephrosis or even multicystic dysplasia may be detected because the ureterocele typically causes some level of obstruction of that renal unit (Fig. 54-6). More concerning are the ectopic or very large ureteroceles that can cause bladder outlet obstruction. This latter group would need to be managed more urgently with drainage. With severely obstructing ureteroceles, or in the presence of infection, drainage with endoscopic incision is usually performed in the first few days of life. Prophylactic antibiotics should be administered because the incidence of VUR after incision of ureterocele is high. In the setting of a nonfunctional kidney with an associated ureterocele, observation and prophylactic antibiotics are appropriate.[19]

Megaureter

Primary megaureters can be divided into three major categories: obstructing; refluxing; and nonobstructing, nonrefluxing megaureters. Many megaureters are detected on prenatal ultrasonography, but they may manifest with infection. Prophylactic antibiotics should be administered until VUR is ruled out by VCUG. Megaureters rarely require emergent treatment. As shown by Confer and colleagues,[20] 72% of lower grade (grade I to III) nonobstructing, nonrefluxing megaureters resolve spontaneously in 12 to 36 months. If infection or severe obstruction is identified along with impaired or deteriorating renal function, surgical intervention in the form of cutaneous ureterostomies is required. This is usually found after the neonatal period and is discussed in further detail in other parts of the text.

Abdominal Mass

An abdominal mass in a neonate is a common finding. More than 60% are urologic in origin with hydronephrosis the most common cause.[21] A thorough physical examination is required to characterize the mass and to identify any other anomalies. The physician should pay particular attention to any limb, facial, or genital abnormalities because many genetic syndromes involve abdominal masses. Ultrasound is very useful in determining whether the mass is cystic or solid. Cystic masses may represent hydronephrosis, multicystic dysplastic kidney, simple renal cysts, polycystic kidney, bladder distention, or adrenal hemorrhage. Solid masses are worrisome for renal vein thrombosis, renal ectopia, and renal or adrenal malignancies.

Renal or Adrenal Mass

Tumors rarely occur in utero, but have been reported. Congenital mesoblastic nephroma is the most common; Wilms' tumors and neuroblastomas also have appeared prenatally.[22,23] Surgery need not occur within the first 24 hours for most neonatal malignancies, but most procedures are performed within the first week (Fig. 54-7).

Renal Vein Thrombus

Renal vein thrombus, although very rare, is the most frequent vascular condition occurring in the newborn kidney. The classic presentation includes the triad of flank mass, gross hematuria, and thrombocytopenia, but this triad is present only about 15% of the time. Presentations may also include hypertension, renal failure, anemia, gross or microscopic hematuria, and leukocytosis with fever. Renal vein thrombus is caused by renal vein stasis from either hemoconcentration or decreased perfusion. Risk factors for renal vein thrombus include dehydration, sepsis, maternal diabetes, polycythemia, birth asphyxia, indwelling umbilical venous catheter, and factor V Leiden. One study found that 43% of neonates with renal vein thrombus had a prothrombotic abnormality.[24] Ultrasound appearance varies depending on the timing of presentation and extent of thrombus, but mostly shows an enlarged kidney with decreased echogenicity, loss of corticomedullary differentiation, and hyperechoic streaks throughout the kidney.[25]

Treatment includes hydration and correction of any electrolyte abnormalities. Some studies have shown an improvement in long-term renal function with the use of heparin therapy,

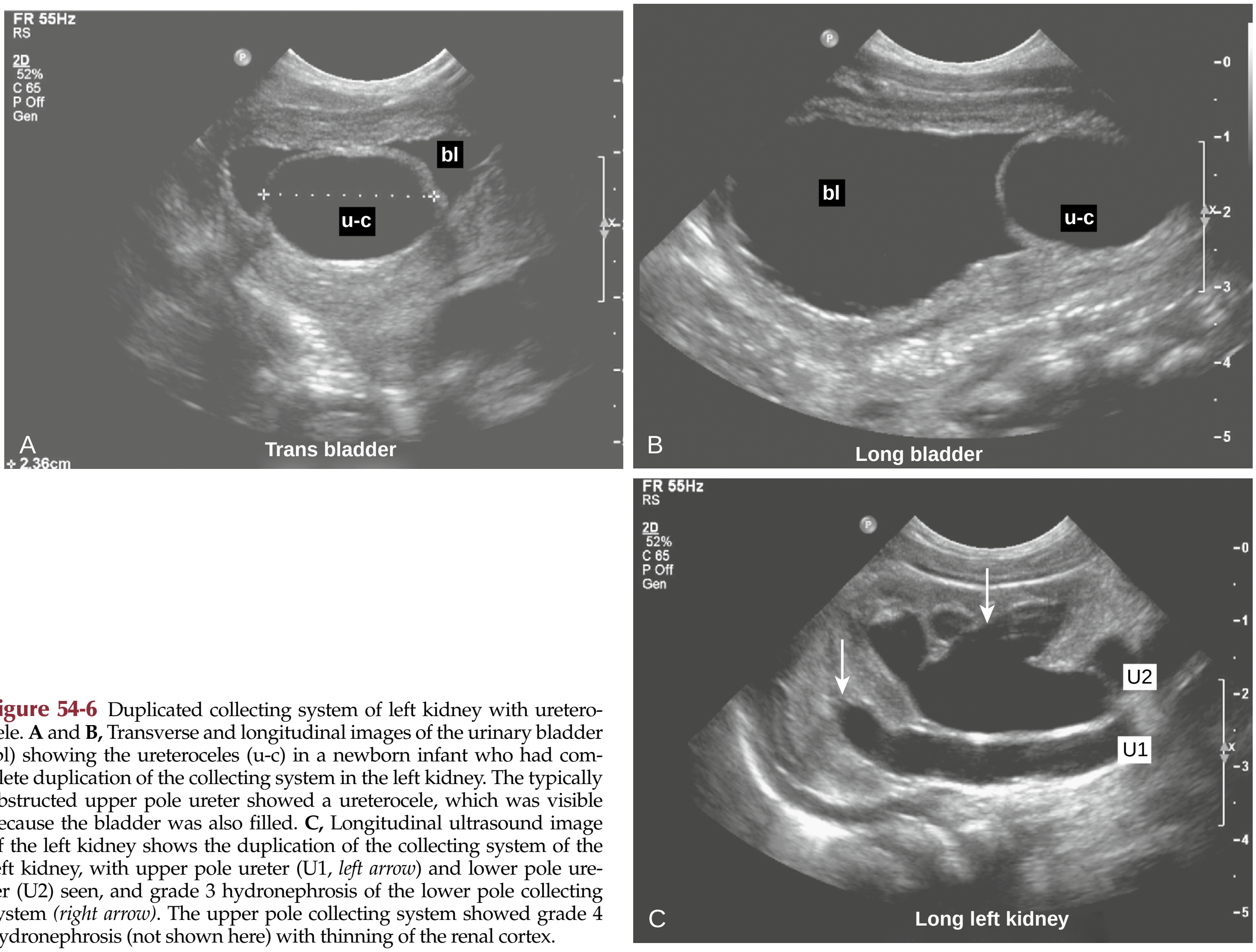

Figure 54-6 Duplicated collecting system of left kidney with ureterocele. **A** and **B,** Transverse and longitudinal images of the urinary bladder (bl) showing the ureteroceles (u-c) in a newborn infant who had complete duplication of the collecting system in the left kidney. The typically obstructed upper pole ureter showed a ureterocele, which was visible because the bladder was also filled. **C,** Longitudinal ultrasound image of the left kidney shows the duplication of the collecting system of the left kidney, with upper pole ureter (U1, *left arrow*) and lower pole ureter (U2) seen, and grade 3 hydronephrosis of the lower pole collecting system *(right arrow)*. The upper pole collecting system showed grade 4 hydronephrosis (not shown here) with thinning of the renal cortex.

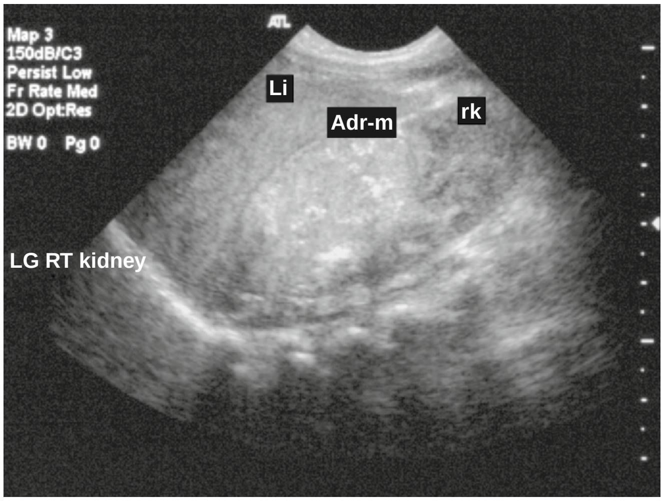

Figure 54-7 Newborn with neuroblastoma. Longitudinal ultrasound image of the right abdomen shows an echogenic mass in the right adrenal gland (Adr-m) causing the right kidney (rk) to be distorted and displaced. Note the liver (Li) located immediately above the right kidney, with which the echotexture of the kidney is usually compared.

although this treatment is controversial.[26] Fibrolytic therapy with streptokinase has also been advocated by some clinicians, but is not without significant complication risks. Overall, approximately 25% of the time the kidney either improves or regains normal function.

Renal Artery Thrombosis

Renal artery thrombosis in a neonate is extremely rare and is mostly associated with umbilical artery catheterization. Only 11 cases have been reported in which an umbilical artery catheter was not involved, and all 11 were in neonates with multiple congenital anomalies or maternal diabetes.[27] Risk factors include sepsis, dehydration, and embolism from patent ductus arteriosus. The most common presenting signs include anuria, hematuria, and gangrene of the extremities; however, less specific presentations, including hypertension, cyanosis, and cold pulseless extremities, have also been reported. Delayed presentations are common even weeks after an umbilical catheter. Duplex Doppler renal ultrasound is an appropriate initial study to provide a noninvasive and accurate diagnosis.

Initial treatment includes anticoagulation with heparin and fluid resuscitation. Intra-arterial antiembolic treatment (the treatment for an adult) is much more difficult because of the

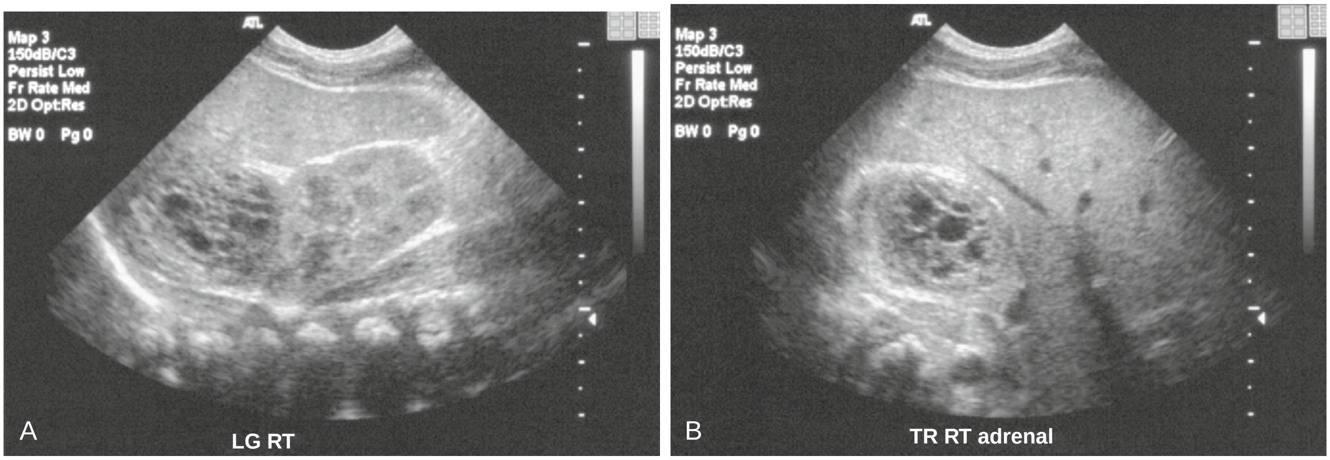

Figure 54-8 Neonate with adrenal hemorrhage. **A** and **B,** Longitudinal and transverse ultrasound images of the adrenal and the right kidney show a solid adrenal mass with numerous small cysts. A few days later, a noncontrast CT scan showed a smaller cystic lesion with calcification in the periphery (not shown here).

small size of the renal vessels. Nephrectomy may be required for refractory hypertension.[28] Even though careful umbilical artery catheter placement—sometimes with the use of anticoagulants—has decreased the incidence of thrombolic events in neonates, renal artery thrombosis should be suspected with these presentations, especially with a history of umbilical artery catheterization.

Adrenal Hemorrhage

Adrenal hemorrhage is common. Although its exact etiology is unclear, risk factors include birth trauma, septicemia, and hemorrhagic disorders.[29] Many hemorrhages are discovered on prenatal imaging. Postnatally, the infant may present with an abdominal mass, anemia, or shock. Acute scrotal swelling or hematoma or both have also been reported as presenting signs in several case reports.[30,31] Adrenal hemorrhage typically appears as a cystic suprarenal mass on an ultrasound scan (Fig. 54-8). The differential diagnosis includes adrenal cysts, adrenal hemorrhage, neuroblastoma, renal malignancies, and renal duplication. A renal ultrasound scan should readily differentiate between most of these entities, although neuroblastoma often cannot be ruled out, and a computed tomography (CT) scan is obtained. A urine collection for homovanillic acid, vanillylmandelic acid, and catecholamines aids in the exclusion of neuroblastoma. Most adrenal hemorrhages resolve without intervention. Involution of the mass on repeat ultrasound scan is the usual clinical course. If the mass fails to show signs of regression by 6 weeks, or in the case of uncontrollable bleeding, surgical resection is appropriate.

OTHER CONDITIONS

Posterior Urethral Valves

PUVs should be suspected in any male infant with a history of bilateral hydronephrosis. PUV is the most likely cause of bladder outlet obstruction in a newborn boy and is the most common urologic cause for renal failure and need for transplantation in children.[32] PUVs manifest with a distended bladder and hydronephrotic, often palpable, kidneys. Abdominal ascites may also be present indicating a forniceal rupture. Renal ultrasound scan reveals varying degrees of bladder dilation with bladder wall thickening and a dilated posterior urethra—the “keyhole” sign. A VCUG should be obtained without delay to confirm the diagnosis. Characteristic VCUG findings include a dilated proximal urethra with a thickened bladder neck (“reverse Ace of spades” sign), valve leaflets evident in the urethra, and VUR in 50% of affected boys (Fig. 54-9). Bladder damage in the form of cells or diverticula or both may also be evident.

Although a normal infant may take 24 hours to void, in the case of PUV, bladder drainage is required immediately. A 5F or 8F feeding tube is ideal for bladder drainage and should be secured with a clear nonconstricting dressing. Foley catheters are not preferred because of the tendency of the balloon to occlude the ureteral orifices and cause bladder spasm leading to a secondary obstruction. One must ensure the feeding tube is within the bladder and not coiled in the dilated prostatic urethra. Either an ultrasound scan or cystogram can determine this. Prophylactic antibiotics are started, and a metabolic panel is obtained to assess renal function. Hyperkalemia and acidosis are common problems in the neonatal period. Depending on the condition of the infant, bladder drainage is often continued for 5 to 7 days, after which endoscopic resection of the valve leaflets may be performed in stable patients. If endoscopic resection cannot be accomplished, a cutaneous vesicostomy is the next step.

Prognosis depends largely on the degree of obstruction, which often correlates with the presence, severity, and timing of oligohydramnios. The degree of renal impairment may not correlate with the grade of hydronephrosis. Failure of the serum creatinine level to decrease to less than 1 mg/dL within the first year is considered a poor prognostic indicator for future renal function. Serum creatinine levels during the first 24 to 48 hours are reflective of maternal function and not that of the infant. Respiratory distress secondary to pulmonary hypoplasia, rather than renal insufficiency, is the principal cause of mortality during the early neonatal period.

Prune-Belly Syndrome

Prune-belly syndrome (Eagle-Barrett syndrome, triad syndrome) is readily identified on physical examination by the thin, lax, “prune” appearance of the abdomen. The diagnostic criteria of abdominal wall musculature hypoplasia, large hypotonic bladder with dilated tortuous ureters, and bilateral cryptorchidism are specific for prune-belly syndrome.

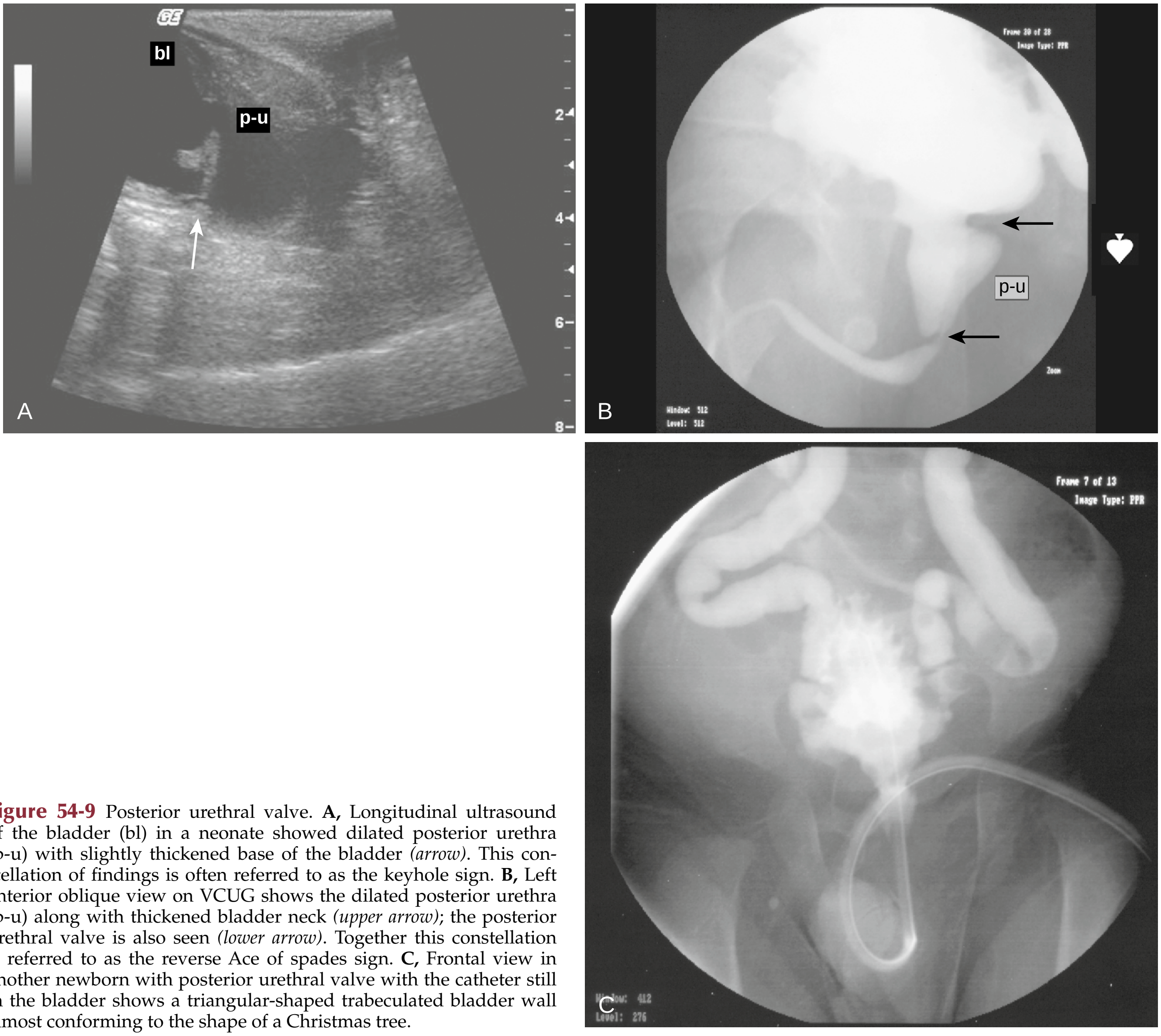

Figure 54-9 Posterior urethral valve. **A,** Longitudinal ultrasound of the bladder (bl) in a neonate showed dilated posterior urethra (p-u) with slightly thickened base of the bladder *(arrow)*. This constellation of findings is often referred to as the keyhole sign. **B,** Left anterior oblique view on VCUG shows the dilated posterior urethra (p-u) along with thickened bladder neck *(upper arrow)*; the posterior urethral valve is also seen *(lower arrow)*. Together this constellation is referred to as the reverse Ace of spades sign. **C,** Frontal view in another newborn with posterior urethral valve with the catheter still in the bladder shows a triangular-shaped trabeculated bladder wall almost conforming to the shape of a Christmas tree.

Associated anomalies include severe urethral stenosis or atresia, megalourethra, and imperforate anus. As with PUV, prenatal megacystis, hydronephrosis, and oligohydramnios are suggestive, although one cannot reliably differentiate in utero between the two. Initial management includes prophylactic antibiotics, serial serum electrolytes, and a renal ultrasound scan to assess renal parenchyma and extent of dilation. Infection rather than obstruction represents the greatest threat to renal parenchyma. Immediate VCUG can be avoided to limit any urethral instrumentation.

If the diagnosis is in question, or if catheterization is performed for any reason, a VCUG can then be performed. A characteristic finding is a large-capacity bladder, often with an elongated hourglass appearance of a wide urachal diverticulum (or pseudodiverticulum); 85% have VUR. A dilated proximal urethra is often seen, which can be difficult to distinguish from PUV. In prune-belly syndrome, prostatic hypoplasia is responsible for the urethral dilation, and a wide bladder neck is seen instead of the bladder neck hypertrophy that is seen in PUV (Fig. 54-10). Although the exact pathophysiology behind the urologic manifestations is not well understood, it is generally believed not to be a true outlet obstruction. Rarely does an infant with prune-belly syndrome need emergent intervention. The immediate problems are usually pulmonary (pneumothorax and pneumomediastinum are common). Renal failure may be evident, however. Any instrumentation of the urethra exposes the child to infections that can be difficult to eradicate; a conservative approach is the best initial choice.

Although approximately 50% void spontaneously, the true bladder function requires an ongoing evaluation. In the setting of deteriorating bladder function or persistent infection, a cutaneous vesicostomy should be considered with plans for future undiversion tailored for the individual patient.

Urethral Atresia

Congenital urethral atresia in a boy results in complete urethral obstruction caused by a constricting membrane usually located in the distal prostatic urethra with accompanying hypoplastic urethra distally.[33] By itself, this anomaly is incompatible with life. Survival is possible, however, if a communication

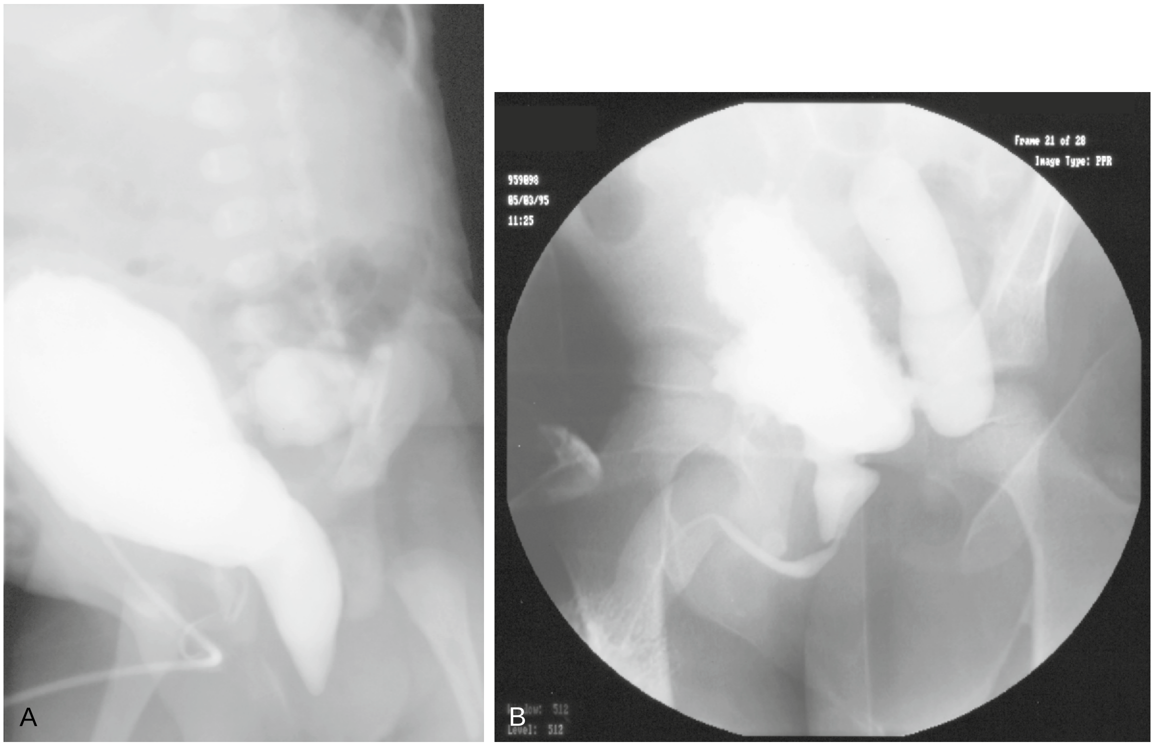

Figure 54-10 Comparison of posterior urethra in prune-belly syndrome and posterior urethral valve. **A,** Left anterior oblique view of the bladder in a patient with prune-belly syndrome shows the dilated bladder and posterior urethra mimicking a posterior urethral valve. Note the bladder is elongated and at the dome (not shown) gives a false impression of urachal cyst or remnant often giving an hourglass appearance. Dilation of the posterior urethra is also seen, and this is due to hypoplasia of the prostate and the lack of thickening of the base of the bladder. This distinctly differs from the appearance of the posterior urethra in a patient with posterior urethral valve **(B). B,** Left anterior oblique view of bladder in a patient with posterior urethral valve shows the thickened bladder neck and dilated posterior urethra; the posterior urethral valve also is seen. Note the distinction in the appearance from **A**.

develops from the bladder in the form of a patent urachus, vesicoamniotic fistula, or vesicorectal fistula. Associated findings include a distended bladder, VUR, and varying degrees of renal dysplasia. It is commonly found in association with prune-belly syndrome. Survival has been reported after vesicoamniotic shunting, but renal impairment is usually severe. Treatment requires urinary diversion usually in the form of a vesicostomy. Serial urethral dilations have been successful, but most cases require future urethral reconstruction.

Myelomeningoceles

A child born with a myelomeningocele defect needs prompt urologic evaluation. Appropriate urologic management is crucial for long-term renal and bladder function. The voiding characteristics are highly variable and tend to change over time. Initial evaluation is required to determine the bladder capacity, voiding potential, and detrusor sphincter synergy. A baseline renal and bladder ultrasound should be obtained immediately along with careful monitoring of voiding pattern. The finding of hydronephrosis and or high postvoid volumes suggests high-pressure systems, which may be a result of bladder sphincter dyssynergia. The immediate urologic concern is to determine whether high voiding pressure exists, in which case the child needs intermittent catheterization. Parents should be counseled about the dynamic nature and unpredictable pattern of voiding function and the importance of continued monitoring.

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For complete list of references log onto www.expertconsult.com

CHAPTER 55

URINARY TRACT TRAUMA

Anthony J. Casale

Trauma is the leading cause of morbidity and mortality in children today and results in more childhood deaths than all other causes combined. Historically, two factors have led to the current importance of trauma in children's health care. Over the past half century, the advent of antibiotics improved treatment of infectious disease, and at the same time society became dependent on the automobile leading to more motor vehicle accidents involving children.

Trauma to the urinary tract is second only to trauma of the nervous system in childhood injuries.[1] Significant trauma to the genitourinary tract is found in 2.9% of children evaluated at pediatric hospital trauma centers.[2] The genitourinary tract may be injured bluntly from falls, motor vehicle accidents, sports injuries, physical assault, and sexual abuse.[3] Sharp or penetrating injuries can result from falls onto sharp objects or from assaults with guns or knives.

The urologist is seldom the first physician to evaluate or treat trauma. Modern management of trauma has evolved into a team activity involving pediatricians, emergency physicians, surgeons, urologists, and other appropriate physicians. Because genitourinary injuries are seldom life-threatening, urologists are generally called as consultants after the initial evaluation has been completed. Although genitourinary injuries may not dominate the initial management period, they often linger on, and the urologist may care for the child for most of the hospitalization. Because of the potentially legal nature of the events that lead to childhood trauma, it is imperative that each physician document the injuries and treatment completely in the medical record. In cases of suspected physical or sexual abuse, the urologist must carefully evaluate and record all information available about the injuries, and contact the local child protective agencies who have the responsibility and authority to complete the investigation.

EVALUATION OF THE URINARY TRACT FOR TRAUMA

The history of the events surrounding the injury is extremely helpful in understanding the mechanism of injury and the possible results. The urologist should question any witnesses of the event about the use of seat belts in cars, loss of consciousness, the height from which falls occur, how and where the patient landed, and the immediate complaints of the injured child. Of special importance are questions about bleeding from the urinary meatus, and if the child voided before being examined. It is important to communicate well with the other team members regarding the extent of the injuries to other organ systems and planned treatment such as laparotomy.

The physical examination can provide a considerable amount of helpful information about the organs injured and the mechanism of the injuries. Abrasions or contusions of the genitalia, abdomen, back, and perineum may document the site of contact that produced the injury. Ecchymosis of the perineum in the shape of a butterfly indicates blood within the limits of Colles fascia that may result from genital or pelvic bleeding. A mass or ecchymosis of the flank may represent a perinephric hematoma or urinoma. Labial or scrotal edema or hematoma may result from genital trauma or from pelvic injuries to the bladder or urethra. Blood from the urinary meatus or vagina can indicate the presence of urethral or vaginal injuries. Abdominal or pelvic masses may represent urinoma or hematoma from injuries to any portion of the urinary tract. A rectal examination may produce important information about the position of the urethra and bladder and possible masses from pelvic hematoma.

The urine should be examined for blood, and hemoglobin and hematocrit values must be obtained to document potential blood loss. The initial blood counts would not accurately reflect blood loss, but can serve as a baseline level for comparison. Blood pressure is not sensitive in children, and they can compensate for blood loss by vasoconstriction and increased cardiac output. Initial blood pressure should always be recorded. When an injured child's blood pressure decreases because of hypovolemia, it does so rapidly and is typically unstable. Tachycardia is a potentially important sign for blood loss and results from the cardiovascular compensation for hypovolemia. Other causes for tachycardia include anxiety from the accident and pain.

Radiographic evaluation of the urinary tract is the cornerstone of management. Complete imaging of the urinary tract provides for accurate staging, management, and prognosis of the injury. The upper tracts including kidneys and ureters are usually imaged today with spiral computed tomography (CT) scanning with good results and few limitations. Because of the rapidity of spiral CT, it may be necessary either to delay the CT scanning or to repeat the scan when the contrast material is visible within the renal parenchyma. CT is best for viewing solid organs such as the kidney, but it does not visualize the ureters adequately. Still, because of the relative infrequency of ureteral injuries, CT is the best initial upper tract imaging tool. The lower urinary tract including the bladder and urethra can be imaged with CT, but it is not accurate unless the bladder is catheterized and filled with contrast material in a retrograde manner.

The retrograde urethrogram is still the best study for imaging the urethra, and the simple cystogram is adequate to evaluate bladder injuries. Rarely, some patients must be taken to the operating room for retrograde pyelograms to evaluate the ureters fully, but this is usually done as a secondary evaluation after initial resuscitation is complete, and other imaging tools, such as CT, ultrasound, or intravenous pyelogram (IVP), suggest a ureteral injury.

RENAL TRAUMA

The kidney is the most frequent site of genitourinary trauma, resulting in half of all urinary system injuries. The kidneys may be injured either with blunt force or by penetrating injuries resulting from gunshots or knives. Kidney injuries occur in 8% to 12% of patients sustaining blunt and penetrating

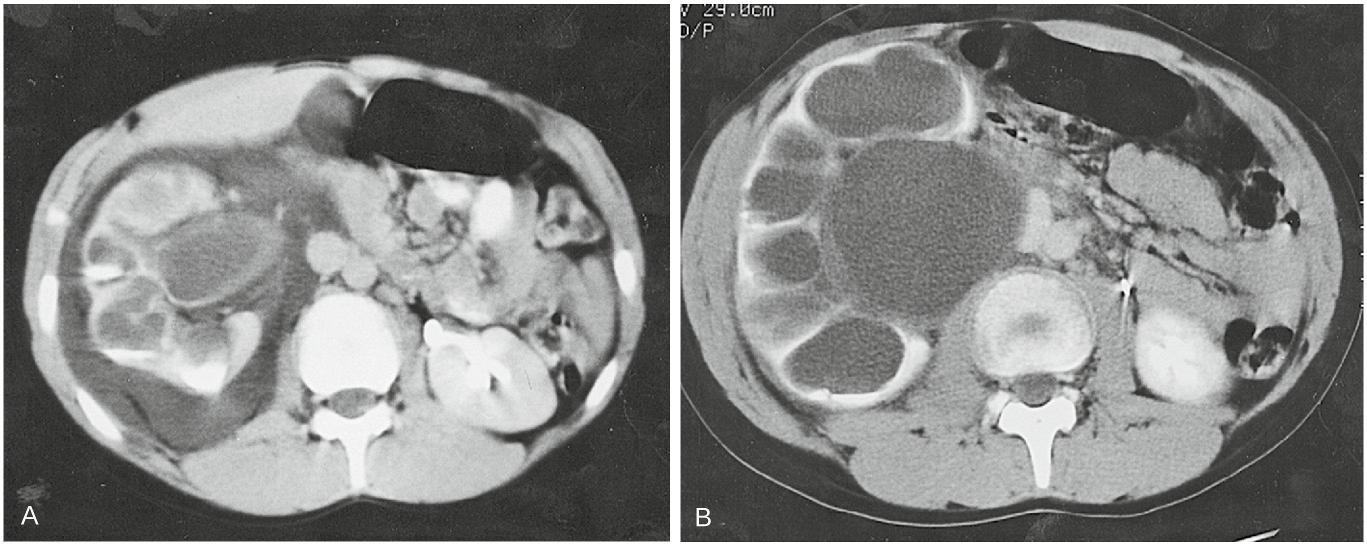

Figure 55-1 **A,** CT scan of a 9-year-old boy injured in a fall reveals a perinephric hematoma and underlying hydronephrosis. **B,** Another CT scan done 6 weeks later reveals that the hematoma resolved, and the hydronephrosis resulting from a ureteropelvic junction obstruction is clearly shown. (From King LR. *Urologic Surgery in Infants and Children.* Philadelphia: Saunders; 1998:266.)

abdominal trauma. Blunt trauma is the most common type of injury to the kidney and represents 80% to 90% of all kidney trauma.[3] The incidence of penetrating renal injuries as a result of violent attacks is increasing rapidly in adults and children, particularly in inner-city adolescent boys.[4,5] In suburban and rural areas, blunt trauma still constitutes most injuries secondary to falls and motor vehicle accidents and produces 90% to 95% of renal injuries.[6]

Blunt Renal Trauma

The kidney in a child is more susceptible to blunt trauma than the kidney in an adult because of different body proportions. The child's kidney is larger than the adult's in proportion to the body cavity and is less protected by the ribs because it projects lower beyond the rib cage. The ribs are more flexible and fail to provide as much rigid protection as in the adult. Abdominal muscles and trunk muscles are less developed and provide less direct protection and rigid support. There is less retroperitoneal and peritoneal fat to buffer injuries to the kidney in children. Some authors have postulated that persistent fetal lobulations found in the kidneys of young children present natural cleavage planes within the renal parenchyma when subjected to the forces of trauma.[4]

Blunt injuries to the kidney in children are most often due to accidents with motor vehicles and falls. In contrast to adults, many children are injured when struck by an automobile. In a group of 129 children with blunt renal injuries 45 (35%) were pedestrians struck by a motor vehicle, 40 (31%) were passengers in a motor vehicle accident, 36 (28%) were injured in falls, 5 (4%) were injured while playing sports, and 3 (2%) were assaulted.[2,7-10] In adults, motor vehicle accidents make up 50%, assaults make up 9% to 17%, vehicle pedestrian accidents make up 11% to 18%, and motorcycle accidents make up 11% of blunt renal injuries.[11,12] Boys sustain blunt renal injuries twice as often as girls. Most series support a slight predominance of the right kidney over the left, but this finding varies.

Congenitally malformed kidneys are more vulnerable to blunt renal trauma than normal kidneys. The incidence of congenital malformations in series of blunt renal injuries varies in different reports from 4% to 23%.[13-15] From a trauma database of almost 15,000 children, McAleer and colleagues[15] found 16 patients with renal injuries in congenital malformed kidneys. Only six patients required surgery; five surgeries were for ureteropelvic junction obstruction, and one nephrectomy was performed for trauma. The most common renal anomalies susceptible to blunt injury are hydronephrosis (38%), tumors (7%), and ectopic kidney (7%).[16] Further evidence of the increased vulnerability of these kidneys is the fact that the injuries have a lower incidence of associated organ injuries, have lower overall injury severity scores, and result from lower velocity accidents. A hydronephrotic kidney may sustain the same injuries as normal kidneys, but is more likely to rupture and lead to extravasation into the retroperitoneum and occasionally into the peritoneal cavity (Fig. 55-1).[17] Rupture of hydronephrotic kidneys may be managed with initial drainage by percutaneous nephrostomy allowing repair of the primary urologic condition later after the effects of trauma have subsided.[18]

Blunt renal injuries in children are seldom isolated, and multiorgan injury is the rule.[18a] Of children with all classes of renal injury, 80% had other associated organ injuries.[2,10] Pedestrian vehicle accidents are typically very violent, as are falls that lead to renal injuries. This type of trauma leads to multiorgan injuries, including other solid abdominal organs such as liver and spleen and neurologic injuries to the head and spine. Surveys of renal trauma in children reveal associated liver or spleen injuries in 46%, closed head injuries in 35%, and orthopedic fractures in 21%.[2,10]

In a child who has sustained blunt abdominal trauma, the physical examination and laboratory evaluation are often helpful in predicting renal involvement. Signs of pediatric renal trauma include abdominal or flank tenderness, lower rib fractures, fractures of the vertebral pedicles, trunk contusions and abrasions, and hematuria. Hematuria has been a reliable finding in children with renal injuries, and only 2.6% of all renal injuries do not have either microscopic or gross hematuria at presentation. Of severe renal injuries, 65% have gross hematuria initially, 32.7% have only microhematuria, and only 1.7% have no hematuria.

Only two types of uncommon renal injury frequently manifest without hematuria: complete ureteropelvic disruptions and renal pedicle injuries to the vessels. Renal pedicle injuries have never been reported as an isolated injury and have been seen only with multisystem trauma.[19] The degree of hematuria does not correlate well with the severity of renal injury. Minor renal contusions may manifest with gross hematuria (31%), microhematuria (65.5%), or no hematuria (3.4%).[2,8-10,20,21] Gross hematuria has been more predictive of significant renal injuries, but even then only 32% of patients with gross hematuria had major renal injury.[17]

The degree of microhematuria in blunt trauma may be important in establishing a threshold for evaluation. The question is which children with blunt abdominal trauma and microhematuria need imaging. There have been several studies on this subject in children looking at various thresholds of microhematuria, such as 20 red blood cells per high-power field (RBCs/HPF) and 50 RBCs/HPF.[22-25] Very few renal injuries were found in children with low levels of microhematuria. Morey and colleagues[19] studied 147 children with microscopic hematuria and a history of abdominal trauma, and found only 1 who had a significant renal injury. They also reviewed 548 patients from the literature and found only 11 (2%) with significant renal injuries and microscopic hematuria with less than 50 RBCs/HPF. All 11 patients had massive injuries that would have required abdominal imaging and would have included the kidneys.

Although the threshold of 50 RBCs/HPF seems a reliable number to define significant microhematuria in trauma, there are many reports of significant renal injuries that manifest with little or no blood in the urine.[26-28] Clear urine alone cannot be used to decide which patients need evaluation for renal trauma. It is important to consider the history of the injury, physical examination, consciousness of the child, and overall clinical status.[29] Awake, alert children who have minimal symptoms or clinical findings suggestive of renal injury and microhematuria less than 50 RBCs/HPF may be observed without CT scans or screened with ultrasonography.

An important difference between children and adults with renal trauma is the reliability of hypotension as a predictor of the severity of injury. Mee and associates[30] reviewed 1007 cases of blunt trauma in adults, and found 44 (4.4%) with significant renal injuries. All of the 44 patients had either gross hematuria or microscopic hematuria and hypotension or shock. Of 812 patients who had neither hypotension (diastolic blood pressure <90 mm Hg) nor gross hematuria, all failed to exhibit a significant renal injury. Other authors have validated these criteria, and currently adults with blunt trauma and microhematuria without hypotension or other clinical findings do not need imaging studies of the urinary tract.[12,31] All patients with gross hematuria who are suspected to have renal injury continue to need imaging studies.

In children, the incidence of hypotension with blunt renal trauma ranges widely. In a review of 197 patients from the literature, the incidence of shock ranged from 5% to 46%, and averaged 16%.[2,8-10,18,32] Of these children, 29% had other intra-abdominal injuries that could account for hypotension. Stein and coworkers[10] reported stable blood pressure in 16 of 17 (94%) children with microhematuria and significant blunt renal injury. Of this group, 53% had other abdominal injuries that led to imaging, which diagnosed the renal injuries, but 44% had no other indications for imaging the abdomen. These children failed to meet the adult criteria of gross hematuria or microhematuria with shock for imaging of the urinary tract, and significant renal injuries would have been missed.

The superior ability of children to support blood pressure in the face of hypovolemia owing to compliance of the vascular tree and cardiac compensation makes hypotension an unreliable predictor of renal injury. We recommend that all children with a history of significant blunt abdominal trauma and any degree of hematuria should undergo imaging of the urinary tract regardless of blood pressure.[33] Although some authors such as Morey[19] suggest observation with bed rest for children with microhematuria and the suspicion of renal contusion, our approach favors imaging, sometimes with ultrasound, to define the injury, if any. Patients may be discharged from the hospital sooner with the knowledge that their injuries are minor and non–life-threatening.[17]

Imaging of the kidneys is performed with CT scanning, and in recent years spiral CT has replaced the older standard CT technology. Spiral CT acquires data using a single continuous x-ray exposure and eliminates errors owing to breathing artifacts. Spiral CT is rapid, and this is particularly helpful with children, who may be uncooperative during the scan. There are limits of spiral CT in detecting collecting system injuries. The scan is typically done 60 seconds after the injection of contrast material and may finish before the collecting system is adequately opacified. Brown and colleagues[34] reported a failure of routine spiral CT scans to detect extravasation of contrast material from 8.6% of a group of 35 patients with blunt renal injuries. These authors suggest that at the end of the initial scan of the abdomen a second series of images of the kidneys would detect extravasation from the collecting system with spiral CT.

Ultrasonography has become an indispensable imaging modality in pediatric urology. Despite the advantages of no radiation exposure, no need for injection, and the ability to perform ultrasound studies without sedation, ultrasonography has been unreliable in evaluating the kidneys in acute trauma. Ultrasound can detect urinomas and hematomas surrounding the kidney, but evaluation of the parenchyma is poor. McGahan and associates[35] studied 32 patients who sustained acute renal trauma with ultrasound and was able to detect only 22% of the injured kidneys. Ultrasonography was better able to detect the more severe renal injuries, but was accurate in only 60% of grade III renal lacerations. The presence of free fluid within the abdomen detected by ultrasound has been associated with renal injury, but this was shown in only 59% of this series, and 63% of those patients had other abdominal injuries that could account for this finding. Ultrasound has a limited place in the evaluation of trauma as a means to follow defined renal injuries and perhaps to help reinforce clinical decisions that the kidneys are uninjured in the case of minor trauma.

CT scanning remains the cornerstone of modern staging of blunt renal injuries, and classification systems of these injuries are based on this technology (Fig. 55-2). Because the mechanism of injury is blunt force applied to the kidney and tearing the parenchyma, the classification system is based on the extent of these tears or lacerations. In the least severe renal injuries, the forces are insufficient to tear the parenchyma. As the forces applied to the kidney increase, so does the severity of parenchymal tearing. The depth of the parenchymal tear into the kidney defines the stages of renal injury, as does the involvement and injury of the collecting system. The most severe forces cause the most severe injuries, such as shattered kidneys and renovascular injuries.

The most common blunt injuries to the kidney, renal contusions, are the least severe and constitute 80% of total renal injuries.[27,28] Previously, these injuries were not detected with older imaging technology, such as IVP. They were diagnosed only with the development of CT and are defined as an area of decreased uptake of contrast material or with a subcapsular hematoma. Patients with renal contusions may present with either gross or microscopic hematuria and may be asymptomatic. They are treated with bed rest until the gross

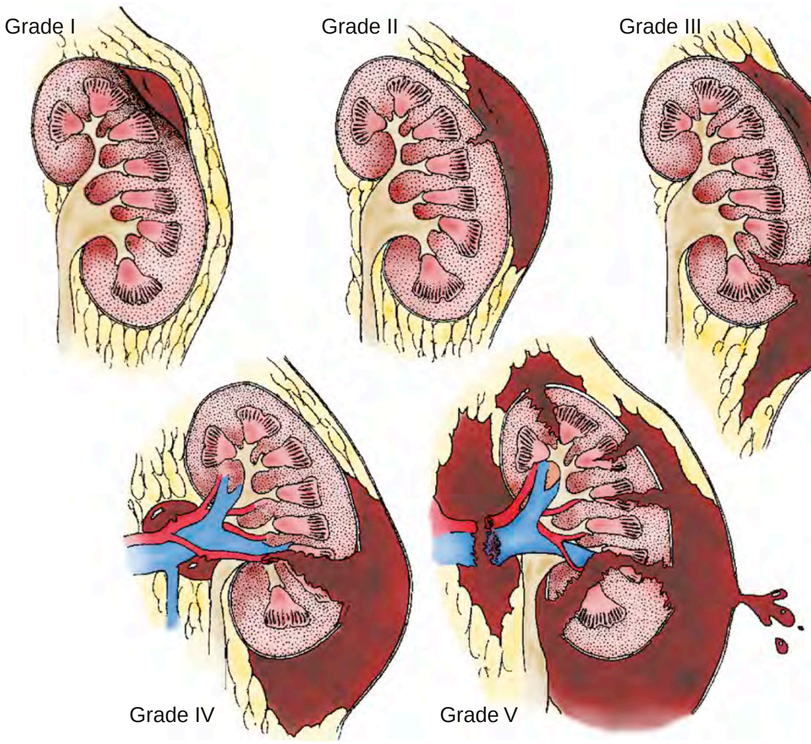

Figure 55-2 Classification system of renal trauma based on the appearance on CT imaging. Grade I and some grade II injuries had not been detectable before the availability of CT. (From Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver, and kidney. *J Trauma.* 1989;29:1664-1666.)

hematuria or symptoms resolve. Follow-up imaging of contusions is generally unnecessary.

The next level of injury to the kidney occurs when the parenchyma tears and separates. These minor lacerations are limited to the superficial cortex of the kidney. These injuries produce more pain and nausea than contusions, and may result in large perinephric hematomas. Lacerations do not enter the collecting system, and there is no extravasation of urine or contrast fluid. Conservative management with bed rest and intravenous fluids as necessary is the accepted treatment. Lacerations take proportionally longer to recover than contusions, and follow-up imaging studies are indicated to ensure that the hematoma does not expand, and that the kidney heals.

More severe lacerations extend further into the kidney and often disrupt the collecting system. Bleeding can be extensive from the parenchyma and may fill the limits of Gerota fascia with a large perinephric hematoma. Patients initially may be hemodynamically unstable until the bleeding stops. If the space within Gerota fascia fills completely with blood, the bleeding may be tamponaded by the hematoma, and the patient may stabilize. Shock is uncommon in children with isolated renal injuries, but the bleeding may persist requiring repeated transfusions. Careful monitoring with blood counts and vitals signs is mandatory. The diagnosis of urinary extravasation may be difficult initially as bleeding continues and urine output is low. Delayed images on CT scans are necessary to make this diagnosis at the time of injury. The contrast fluid may appear as a swirl of radiodense material spread within the hematoma (Fig. 55-3). These patients need bed rest for 7 to 10 days until pain and hematuria clear, and imaging shows stabilization of the injury.

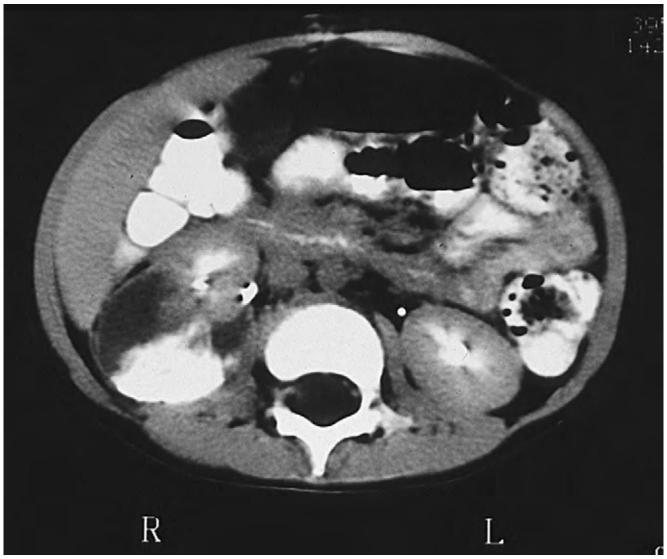

Figure 55-3 CT scan of a child who sustained a major laceration of the kidney from blunt trauma and the resulting extravasation of contrast material into the perirenal space.

Even more force applied to the kidney results in wide separation of the lacerated fragments and a shattered kidney. There is massive bleeding and urine extravasation often filling the limits of Gerota fascia. The segments usually retain their blood supply and remain viable. If bleeding stops, and the patient stabilizes, the kidney may reconstitute itself with time, and the segments heal together in good alignment. If there is a devascularized segment, some authors have found an increased risk of complications with conservative management and advocate early repair and débridement.[36,37] Other authors have not found a devascularized renal segment a negative influence on successful conservative treatment.[38] It is difficult to determine function soon after the traumatic event, and some segments do not appear to take up contrast material during the initial CT study because of contusion. Many of these renal segments function if given time to recover.

Previously, there was a considerable debate over surgical versus nonsurgical management for shattered kidneys or kidneys with severe lacerations. Immediate surgical exploration and repair gives excellent results for some surgeons and still has a role in some circumstances.[14,39] Early repair has been shown to lead to a higher nephrectomy rate than conservative management, however, in the experience of others.[40]

Conservative, nonoperative management with bed rest, fluid resuscitation, and monitoring has become the standard for blunt trauma. The patient is spared the stress and risks of an emergency operation in the period just after the injury.[21] Bauman and colleagues[21] have developed criteria for early surgical intervention after blunt renal trauma. Absolute indications for surgery include persistent bleeding into an expanding or unconfined hematoma. Relative indications include massive urinary extravasation and extensive (>20%) nonviable renal tissue.

McAninch and coworkers[41] reviewed 1193 patients with blunt renal trauma and judged them with these criteria. They found 31 patients (2.5%) who needed immediate exploration. In more recent series of children with blunt renal trauma, 87% to 98% were successfully managed nonoperatively, and with 99% renal salvage rates and 93% of patients having normal blood pressure and renal function on follow-up evaluation.[13,42,43] Among the most severe (grade IV and V) injuries (Table 55-1), Barsness and associates[44] found no difference in long-term outcomes of blood pressure, need for dialysis, or renal insufficiency in a series of 13 patients, in which 7 were treated surgically and 6 were treated nonsurgically. In a review of a trauma database containing 1800 injured children, 4% of patients who were originally treated nonoperatively failed conservative management and required later surgery.[45]

Table 55-1 **Renal Injury Grading Scale**

Grade	Description
I	Contusion with hematuria, urologic studies normal or subcapsular hematoma without laceration
II	Nonexpanding perirenal hematoma or <1 cm laceration without extravasation
III	>1 cm laceration without collecting system involvement or extravasation
IV	Laceration extending into collecting system, urinary extravasation, or injury to hilar vessels with contained hemorrhage
V	Shattered kidney or major hilar injury with devascularization

Based on the renal injury scale of the American Association for the Surgery of Trauma: Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver, and kidney. *J Trauma.* 1989;29:1664.

The management of urinary extravasation has become more conservative as well and is seldom an indication for immediate surgery. Matthews and colleagues[46] studied 31 patients with urinary extravasation resulting from major renal trauma and compared them with renal trauma patients without extravasation. These authors found that the extravasation spontaneously resolved in 87%, and that the remaining patients required only a ureteral stent to clear persistent extravasation. There were no complications, and hospital time was similar. Mansi and Alkhudair[47] reviewed 108 patients with severe renal injuries (including 43 children) and found only 2 with enlarging urinomas. They were treated only with percutaneous drainage of the urinoma with complete resolution (Fig. 55-4). Thompson-Fawcett and Kolbe[48] reported 142 cases of pediatric renal trauma, including 17 with disrupted collecting systems and extravasation. In 10 cases, the extravasation rapidly resolved, but 7 patients developed persistent urinomas. Two resolved after long periods of waiting, but five patients required surgery, one after becoming infected. These authors concluded that if the urinoma does not begin to resolve by 5 days some intervention is indicated. We have used indwelling stents or percutaneous drains or both with good results.

Renovascular Injuries

Renovascular injuries secondary to blunt trauma are unique in that the renal parenchyma is usually not traumatized. These rare injuries involve the renal artery and occur in 1% to 3% of all blunt renal traumas.[49,50] The mechanism of injury is rapid deceleration of the kidney and stretching of the renal

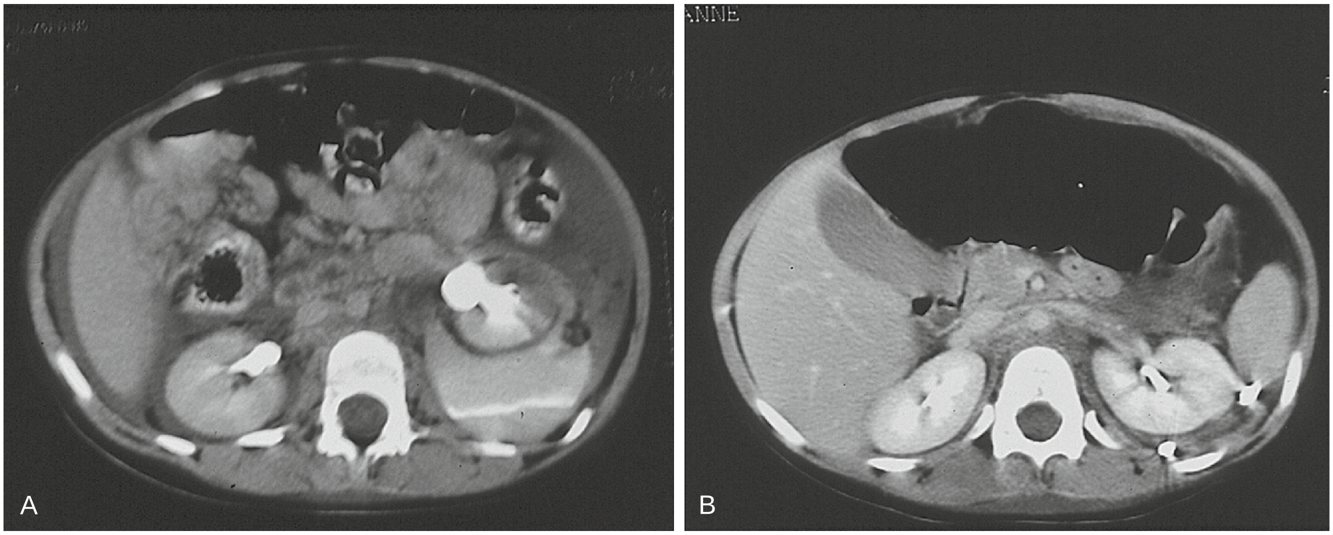

Figure 55-4 **A,** A child was crushed by a piece of construction equipment and sustained a renal injury that resulted in formation of a urinoma. **B,** The urinoma was treated with percutaneous drainage, but extravasation continued until a double-pigtail stent was placed to assist renal drainage.

artery. Other forms of renal injury are due to direct trauma to the kidney. While traveling at a high rate of speed, the body is brought to an abrupt stop by the traumatic event, and the kidneys continue to move until the renal vessels stop them by tethering them to the great vessels that are fixed in the retroperitoneum. The adventitia and muscularis, both of which are elastic, absorb this extreme stretching force to the artery. The intima is not so compliant and tears, exposing the muscularis to the rapid blood flow and raising flaps of intima, ultimately leading to clotting of the artery and ischemia of the kidney (Fig. 55-5).

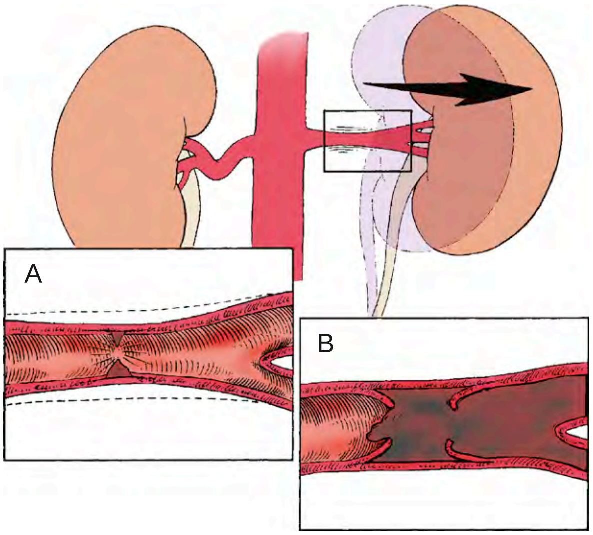

Figure 55-5 **A** and **B,** Mechanism of injury to the renal artery secondary to deceleration and stretching. The adventitia and muscularis of the artery stretches, whereas the intima lacks elasticity and tears. Disruption of the intima exposes the subendothelial tissue to the blood flow and promotes clotting of the artery. (From Peters PC, Bright TC III. Blunt renal injuries. *Urol Clin North Am.* 1977;4:18.)

Hematuria may not be present in renal pedicle injuries, but they are almost always associated with injuries to other organs. The kidney appears intact and normal on CT scan with the exception of its lack of perfusion.[51,52] The CT image usually shows only a dark kidney without perinephric bleeding, and sometimes retrograde filling of the renal vein from the vena cava is observed.[53] If the CT scan shows a nonperfused kidney after blunt trauma, an immediate arteriogram should be obtained to investigate the renal vasculature (Fig. 55-6). Some authors argue that an arteriogram is unnecessary and wastes time that could be helpful in recovering the kidney. They believe that CT scanning is adequate to diagnose a renal pedicle injury, and the next step should be immediate surgical exploration and repair.[44]

Although it would seem to be an easy decision to move to surgical repair to salvage a kidney if possible, this is seldom the case. The overall condition and stability of these patients with multiple trauma frequently makes immediate surgery a significant risk. If the contralateral kidney is normal, and the patient is unstable, it may be wise not to attempt to salvage the ischemic kidney. The time since injury is important because warm ischemia time determines the survivability of the kidney. If the kidney has not been perfused in more than 6 hours, the kidney would not survive even with successful surgical repair. The blood supply is not interrupted to the kidney at the exact time of injury in every case. In a patient with good contralateral kidney function, and who is a good surgical candidate, exploration within 12 hours of the injury is considered reasonable.[44] The best salvage rate for kidneys with pedicle injuries in ideal circumstances is only 30%.[54,55] Other types of renovascular injuries are direct full-thickness tears of the artery and vein. They are rare, require immediate surgery, and have a very high mortality.

Complications of blunt renal trauma occur early and late after the injury. Early complications include hemorrhage, hypertension, urinoma, infection of hematoma or urinoma, and hydronephrosis. These complications occur in 30% of patients who sustain severe renal lacerations and renal fractures.[19,56] Complications are rare in less severe renal trauma.

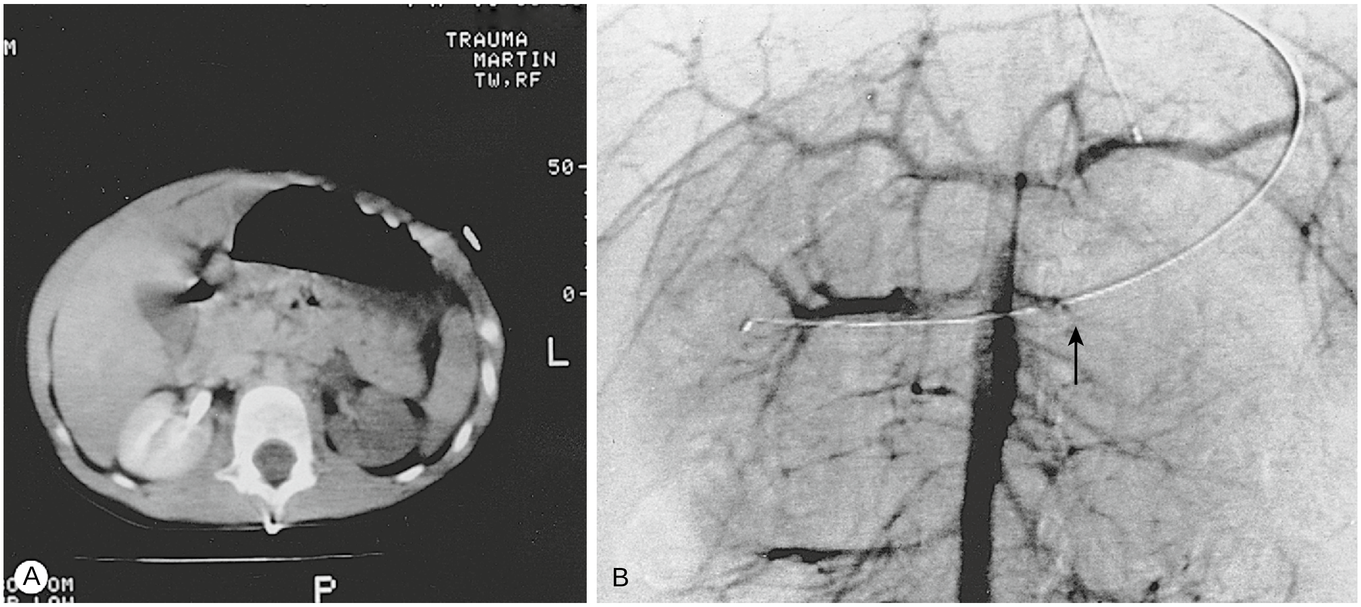

Figure 55-6 **A,** CT scan after blunt trauma shows no apparent perfusion of the left kidney in a child involved in a motor vehicle accident. The size and contour of the kidney are normal, and there is no perirenal bleeding. **B,** Arteriogram shows complete occlusion of the left renal artery. Surgical exploration revealed an intact artery with an intimal tear and subsequent infarction of the kidney. (From King LR. *Urologic Surgery in Infants and Children.* Philadelphia: Saunders; 1998:269.)

Because early complications are so common in severely injured kidneys, it is important to obtain imaging studies during the first week to determine if hematomas or urinomas are enlarging. Abdalati and coworkers[55] reported a series of 23 patients with grade III and IV renal trauma and found complications in 26% with 17% requiring surgery to deal with complications after failure of initial conservative management. Today many of these early complications can be treated with percutaneous drainage procedures. All patients with renal trauma regardless of the initial stage should undergo immediate imaging studies if they develop prolonged or increasing abdominal pain, fever, nausea, hypotension, or hypertension. Patients who sustain grade I or II renal injuries and who do well clinically generally do not need follow-up renal imaging.

The late complications are similar to complications that occur early on, and include delayed hemorrhage, urinoma, hypertension, hydronephrosis, calculi, pseudoaneurysms, renal scars, and loss of renal function.[57] As with early complications, high-grade severe injuries are most likely to develop late problems.[58] Renal scarring and loss of function are common after severe renal injury. A long-term study by Yale-Loehr and colleagues[59] of five patients with severe renal trauma revealed the kidneys lost an average of 12% function because of trauma with a mean percentage of total renal function of 38%.

Devascularized renal segments or entire kidneys need not be removed unless they cause problems. Most often the devascularized segment contracts along with the hematoma as the kidney heals. Abdalati and coworkers[55] studied six children who had pedicle injuries with completely infarcted kidneys. One child acquired an infection that required removal of the dead kidney, and the remaining five recovered without surgery. It is important to follow these infarcted kidneys or renal segments with repeated imaging. If the patient does not recover rapidly or at any sign of infection, a nephrectomy or partial nephrectomy should be performed.

LONG-TERM RENAL OUTCOMES

In recent years, there has been more interest in long-term outcomes of renal trauma. There is almost uniform agreement that in unilateral blunt renal trauma, blood pressure and overall renal function are almost always normal when measured within the first few years after injury. The long-term effects on the injured kidney have been studied and are not as encouraging. Some kidneys show reasonable preservation of function after high-grade blunt trauma with split function of 41% to 50% on technetium 99m dimercaptosuccinic acid (Tc^{99m}-DMSA) renal scans, but almost all show morphologic changes in the form of scarring and occasional cyst formation.[60]

Keller and associates[61] showed split renal function loss proportional to the grade of original injury with 45% function for grades II and III, 42% for grade IV, and 30% for grade V. Functional loss in the damaged kidney may be progressive over time in the case of severely traumatized kidneys. Moog and colleagues[62] found that Tc^{99m}-DMSA scans done 8 days after trauma showed an average 36% difference in the damaged and normal kidney compared with a 48% difference when measured 6 months later. They looked for evidence of compensatory renal hypertrophy by the normal kidney and found none, worsening the long-term prognosis for global renal function. These findings indicate that despite normal blood pressure and overall renal function in children who sustain significant renal trauma in the first few years after injury, these injuries may lead to problems years later. We believe that children who sustain such injuries should undergolifelong blood pressure monitoring and routine urinalysis to look for proteinuria owing to renal deterioration.

PENETRATING RENAL TRAUMA

Penetrating renal trauma has become more common in children and adolescents as a result of increasing societal violence, especially in cities.[63] Hall and colleagues[4] described the increase in penetrating trauma as "the new epidemic in children." Their review revealed that hospital admission for penetrating injuries in children increased 80% in 7 years to make up 36% of admissions to Cook County Hospital in Chicago.[4] In the adolescent group of 12 to 15 years of age, penetrating trauma mostly from street violence was responsible for 66% of admissions. Although gunshot wounds are the dominant form of renal injury, stabbing has become more common as a result of street violence.

Penetrating renal injuries are almost all stab injuries or gunshot wounds. The mechanisms of injury are different, as are the consequences to the kidney.[64] Stab wounds and low-velocity gunshot wounds cause precise localized trauma to the kidney and little collateral damage to the surrounding tissue; this allows for accurate evaluation of the extent of the injury at the time of initial evaluation. High-velocity gunshot wounds cause damage at a considerable distance from the point of impact. These injuries cause contusion of adjacent tissue, and the viability of this injured tissue is difficult to judge for days after injury until some reversible damage has begun to heal. It is tempting to look at poorly perfused renal parenchyma on the initial CT scan and believe it is nonviable, when in fact this tissue may recover function.

Renal Stab Wounds

The history and physical examination in patients with potential penetrating renal injuries offer more information to the examining physician than in blunt renal trauma. The weapon, the skin wound, and the location of the wound all offer helpful information about the potential renal injury. In all stabbings that could potentially injure the kidney—in the lateral abdomen, flank, or lateral back—the kidney is damaged in only 15%. The highest risk of injury to the kidney occurs when the patient is stabbed in the flank, the area between the anterior and posterior axillary lines. Eastham and coworkers[11] reviewed 244 stabbings that could potentially injure the kidney, and found that 75% of all renal injuries resulted from stabbings in the flank, with only 12.5% of renal injuries resulting from stabbings in the abdomen or back.

Most renal stab wounds cause minor kidney injury. Only 23% to 33% of stabbings cause major parenchymal injury, and another 23% cause significant vascular damage. Of patients with renal stab injuries, 12% to 43% have associated organ trauma, most commonly to liver, spleen, and colon.[65,66] Stab wounds posterior to the anterior axillary line have the lowest incidence of intra-abdominal injury (12.5%).[67]

Hematuria is present in most patients with stab injuries to the kidneys, but the degree of hematuria does not correlate well with the severity of injury.[52] Armenakas and colleagues[66] reviewed 200 renal stab injuries and found that 26% did not have hematuria on presentation. In a series of 244 patients who had stab wounds that could potentially involve the kidney, Eastham and associates[11] found 46 with microhematuria and 14 with gross hematuria. They were evaluated with IVP, and 52% of patients with microhematuria and all patients with gross hematuria had renal injuries detected. Along with the position and appearance of the stab wound, other signs of potential renal stab injury include flank tenderness, a flank mass, and hemodynamic instability.

Historically, renal stab wounds have been staged using IVP with an accuracy of 96%.[54] CT has not been as helpful in stab injuries to the kidney as in blunt renal trauma because stab wounds seldom cause extravasation or separation of renal parenchyma. Angiography has been useful because of its accuracy in diagnosing vascular injuries and its potential usefulness as a therapeutic tool to control bleeding.[68] In the San Francisco experience of 200 renal stab wounds, 96 were evaluated with IVP, 69 with CT, and 22 with IVP and CT, and only 6 needed angiography.[56] It seems reasonable to perform either IVP or CT as an initial study depending on the patient's clinical examination and the location of the wound.

Management of renal stab injuries has become progressively more conservative, and fewer patients need immediate surgery. Of all patients with renal stab injuries, 37% to 45% require surgical treatment.[55,56] All patients with isolated minor renal injuries, either on IVP or CT staging, and without signs of significant bleeding may be managed with bed rest and monitoring.

The importance of accurate initial staging is shown by a study of 60 renal stab wounds managed with bed rest in which the complication rate was 20%.[55] The complications were almost exclusively vascular and ranged from secondary hemorrhage to bruits from vascular fistulas, and may have been avoided if the initial injury was better defined by angiography. The relative usefulness of CT or angiography seems to vary among reports and reflects institution strengths and preferences. Armenakas and colleagues[66] found that 3 of 111 renal stab wounds treated nonoperatively eventually required surgery for delayed bleeding within the first 5 days for a complication rate of 2.7%. This experience included 12 patients with more severe injuries (11 grade III and 1 grade IV).

Severe renal stab injuries that include extravasation of urine and extensive renal parenchymal damage usually require surgical exploration and repair. Reviews of patients sustaining severe renal stab injuries reveal that 9% to 12% undergo nephrectomy, and the remainder need repair and drainage on initial surgery.[38,66] There is increased interest in avoiding initial surgery, and current absolute indications for initial surgical intervention include signs of associated intra-abdominal injuries such as peritonitis and hemodynamic instability.[66,69]

Angiography has been useful in the management of renal stab injuries as long as the patent is stable and can undergo the procedure safely. Eastham and colleagues[11] reported that 14 of 16 patients had successful treatment of persistent renal bleeding with angiographic embolization. The two remaining patients required heminephrectomy to control bleeding after unsuccessful embolization. There were two significant complications of the embolization, including loss of one kidney requiring nephrectomy for hypertension.

Gunshot Injuries of the Kidney

Although gunshot wounds to the kidney constitute less than 5% of all renal traumatic injuries, there has been an increase more recently as a result of increased urban violence. Gunshot wounds differ significantly from stab wounds to the kidney. Gunshot wounds produce much more local kidney injury because of the blast effect from the high-energy projectile and are more likely to produce associated organ injuries. Patients who sustain gunshot wounds are generally more severely injured and more likely to be hemodynamically unstable. In comparing the relative severity of injury from stab wounds to the kidney with gunshot wounds, the mean transfusion requirement in two large series was 1978 mL in 95 renal stab wounds and 3742 mL in 87 renal gunshot wounds.[58,60]

As with stab wounds, the location of the gunshot wound can give some insight into the possibility of renal injury. Of all gunshot injuries to the kidney, abdominal wounds account for 54%, flank wounds account for 36%, chest wounds account for 20%, and back wounds account for 11%.[70] Signs of renal injury are the same as with stab injuries and include flank tenderness, flank mass, and hematuria. McAninch and associates[70] reviewed 87 gunshot wounds to the kidneys, and found 50% had gross hematuria, 29% had microhematuria, and 13% had no hematuria.

There is a high incidence of associated organ injuries with renal gunshot wounds. In the San Francisco series, 94% of renal gunshot injuries had other intra-abdominal injuries, including small bowel (38%), colon (38%), liver (33%), stomach (30%), and spleen (23%). When the severity of renal injury was reviewed, 32% had minor renal lacerations and contusions, and 68% had severe injuries to the kidney.[70] For these reasons, a CT scan is necessary to evaluate all gunshot wounds that might involve the kidney. The sensitivity of CT scanning in gunshot renal injuries was found to be 90.5% and the specificity was 96% in a series of 100 hemodynamically stable patients who were considered candidates for nonoperative management.[71] CT findings resulted in a change in management in 40 patients. In contrast to stab wounds, it is common for the patient to be too unstable for complete radiographic evaluation, and in the series by McAninch and associates,[70] 24% of patients required emergency surgery before adequate imaging.

As with renal stab injuries, current management of renal gunshot wounds is becoming more conservative, and many are managed without initial surgical exploration. Renal contusions and minor lacerations of the kidney caused by gunshot may be managed with bed rest and support.[72,73] More severe lacerations and vascular injuries have a high complication rate, mostly from delayed bleeding, if treated conservatively. Because of the complexity of the renal injury and of associated organ injuries, most gunshot wounds of the kidney have undergone exploration. McAninch and associates[70] explored 79% of 87 patients with gunshot wounds to the kidney and found 11 minor renal injuries; 46 underwent renal reconstruction, and 12 underwent nephrectomy because of irreparable renal damage. Even with early exploration, there were four complications, including late hemorrhage and wound infections.

Absolute indications for surgery in gunshot wounds to the kidney include any evidence of persistent renal bleeding, including expanding hematoma, decreasing blood indices, hypotension, and persistent gross hematuria. Relative indications for surgical intervention include extravasation of urine and nonviable renal tissue on CT scan. Modern management of patients with gunshot wounds involving the kidney has resulted in salvage of the injured kidney in 86% and 94% patient survival.[70] Isolated renal injuries, no matter how severe, are rarely a cause of mortality.

SPORTS PARTICIPATION AFTER RENAL INJURY

Participation in team sports and organized sports for children has increased in recent years. The question of increased risk for injury to children with solitary kidneys or damaged kidneys has become a common one in pediatric urology practices. Parents, children, coaches, and school administrators would like answers regarding the safety of this participation; this is often an issue of liability and has legal ramifications. Current knowledge is based on a few studies that quantify risk of renal injury based on reported mechanism of injury. McAleer and colleagues[74] reported the results of a trauma base with 14,763 injured children and 193 renal injuries; 113 (54.1%) injuries occurred during recreational or team sport activity, and only 10 (6%) injuries occurred during organized team sports. There were only three associated injuries, and no organs were lost.

The sports responsible for significant renal injury are specific to geography and may be changing with the popularity of new sport activities. In a review of 14 cases of sport renal injuries, Gerstenbluth and coworkers[75] found that the most common sport causing blunt renal injury was bicycle riding (57%). The historically accepted sport causes of renal trauma of football, hockey, and sledding collectively made up the remaining six cases. The injuries sustained on bicycles were on average much worse, with five of eight resulting in grade IV or V injuries compared with only one of six in the remaining sports. The popularity of all-terrain vehicles and extreme sports such as rock climbing may begin to play a larger role in the etiology of renal trauma.

Team sports seem to be declining as a cause of significant renal injuries, and the injuries sustained while participating in team sports are most often less severe than the injuries that are due to motor vehicles, falls, and bicycles. Although the risk may be low, these activities are not without risk, and in the case of a child with a solitary kidney, the loss of this organ would be life-altering. The pediatric urologist should inform all parties of what is known of the relative risks and potential consequences, and allow the responsible individuals to make the final decision about participation and to take the ultimate responsibility for potential consequences.

RETROPERITONEAL HEMATOMAS

In the case of severe trauma, the urologist may be consulted to evaluate a retroperitoneal hematoma found at the time of emergency laparotomy. Without a preoperative IVP or CT scan, the urologist has no information about the function of the kidneys or the extent of damage to the kidney within the hematoma. This scenario occurred 24% of the time in the San Francisco series of renal gunshot wounds because the patient was too unstable to undergo imaging of the kidney before surgical intervention. In these cases, a single-shot intraoperative high-dose IVP can be performed on the operating table. Although suboptimal for visualization of the kidneys, this study can provide important information to help with management decisions. The status of the contralateral kidney can be established, and the surgeon may avoid opening a retroperitoneal hematoma if the IVP shows an intact and functioning kidney within the hematoma.[76] The decision to explore a retroperitoneal hematoma rests on the characteristics of the hematoma, the presence or absence of hematuria, findings on the IVP, and the mechanism of renal injury.[64]

Expanding or pulsatile hematomas of the retroperitoneum must be explored, as should hematomas associated with severe injuries visible on IVP. The findings of gross hematuria or injury from a high-velocity gunshot wound should encourage exploration of the hematoma. In the case of blunt injuries, stab wounds, or low-velocity gunshot wounds, management may be more conservative. If the IVP shows an intact functioning kidney, and the hematoma is stable, it need not be opened.

If the physician believes that the hematoma must be opened, the surgical technique is important. Although there is some controversy, most authors believe that the initial maneuver should be to control the renal vessels before opening the hematoma.[77] A midline incision in the posterior peritoneum allows visualization of the great vessels and isolation of the renal artery and vein. The hematoma is opened laterally along the white line of Toldt, the colon is reflected medially, and Gerota space is entered to inspect the kidney (Fig. 55-7).[78]

On the other side of this argument are authors who believe that dissection of the great vessels and the renal vessels is time wasted from the midline incision. They take a direct approach by reflecting the colon and opening Gerota fascia and mobilizing the kidney and renal vessels from the lateral approach.[79,80] Critics of this approach cite concerns about the risk of excessive bleeding resulting from releasing the pressure within Gerota fascia before having vascular control. Either technique is efficient in the hands of surgeons who are experienced and comfortable with them. Any opening of a retroperitoneal hematoma is likely to be a bloody and potentially risky experience for the patient and the kidney.

TRAUMATIC URETERAL INJURIES

Injury to the ureter occurs from trauma and from surgical injuries resulting from pelvic surgery. Most ureteral injuries in children are due to trauma, in contrast to adults, whose ureters are more likely to sustain surgical injury. We address only traumatic injuries of the ureter. Most traumatic injuries to the ureter occur in the upper portion.

Any injury to the ureter is rare. The ureter is protected by its close approximation to the vertebral column and paraspinal muscles, and its course within the bony pelvis. The ureter is a small target and is inherently flexible and mobile. The incidence of ureteral injury is less than 1% of all cases of civilian urologic trauma and 9.5% of cases of modern military urologic trauma.[81,82] Penetrating trauma to the ureter is more common than injuries caused by blunt trauma.

Penetrating Ureteral Trauma

The most common type of ureteral injury is due to gunshot wounds, and these injuries constitute 95% of all ureteral trauma.[81] Civilian gunshot wounds to the abdomen injure the ureter 2.3% to 17% of the time.[83] Ureteral injuries are accompanied by associated intra-abdominal organ injury in 97% of cases.[84] Other than injuries causing profound hypovolemia, these associated injuries have little effect on the management or outcome of ureteral trauma.[85]

Stab wounds with knives are the second most common cause of ureteral injury. Patients with ureteral injuries may experience a delay in diagnosis in 57% of cases.[86] IVP and CT scan are inaccurate in exposing ureteral injuries, and may miss the diagnosis in 70% to 75% of cases. IVP has a false-negative rate of 33% to 60%.[87,88] The most reliable method to diagnose ureteral trauma is direct visualization at the time of surgery and retrograde pyelogram. Hematuria is present in only 23% to 45% of patients with ureteral injuries.[71] The best approach is to maintain a high index of suspicion of possible ureteral injury and to obtain delayed imaging in patients with unexplained abdominal findings after penetrating flank trauma.[89]

Blunt Ureteral Trauma

Blunt injury to the ureter is very rare. The most common type of ureteral injury resulting from blunt trauma is the avulsion of the ureter from the renal pelvis at the ureteropelvic junction.[90,91] The proximal ureter also may be disrupted from blunt injury.[92,93] Most blunt ureteral injuries occur in children because a child has a much more flexible trunk and spinal column. The mechanism of injury is extreme hyperextension followed by sudden deceleration and ureteral compression against a vertebral body (Fig. 55-8).[76]

Ureteral injuries are the result of severe trauma and often occur when children are struck by motor vehicles. Sixty

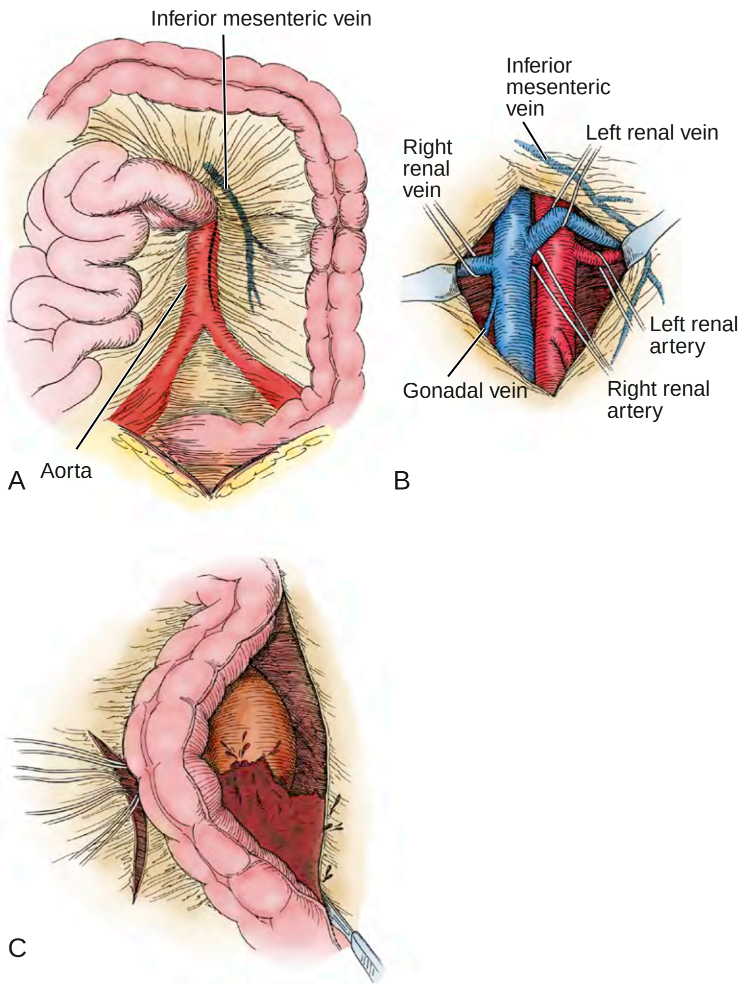

Figure 55-7 Surgical approach to the renal vessels in renal trauma. **A,** A retroperitoneal incision is made over the aorta. **B,** The anatomy of the renal vessels from this exposure. **C,** Exposure of the injured kidney through a second retroperitoneal incision made lateral to the colon. (From McAninch JW. Surgery for renal trauma. In: Novick AC, Pontes ES, Streen SB, eds. *Stewart's Operative Urology*. 2nd ed. Baltimore: Williams & Wilkins; 1989.)

percent of ureteropelvic junction disruptions are diagnosed late when complications occur.[94] Hematuria is an unreliable sign and is absent in 31% to 97% of cases.[76,79] Initial imaging studies, such as IVP and routine CT scans, are unreliable. The diagnostic accuracy can be improved by performing a delayed scan 5 to 8 minutes after injection of contrast material.[95] CT signs include medial extravasation of contrast material and transverse process fractures.[96] IVP with late films may detect the injury, but retrograde pyelogram is the most sensitive examination. Presti and coworkers[94] reviewed 11 disruptions of the ureteropelvic junction, and found that 72% had normal or nondiagnostic IVP on initial studies.

Even surgical exploration can be misleading if the retroperitoneum is not opened and the kidneys examined directly.[64] Most patients have presented several days after injury when the urinoma produces flank and abdominal pain, nausea, and fever. The symptoms are often vague, and the surgeon should remain suspicious about potential undiagnosed urinary injury after significant blunt abdominal trauma in a child.

Treatment of Ureteral Injuries

Similar to all other non–life-threatening urinary injuries, conservative initial management of ureteral trauma has become the rule. Because most ureteral injuries are diagnosed late after the traumatic event, immediate repair during abdominal exploration is rare, and minimally invasive treatment has become more popular. Percutaneous drainage of urinomas and nephrostomy tube drainage have been successful in penetrating and blunt injuries of the ureter. Al-Ali and Haddad[97] reported a series of 46 patients with ureteral injuries treated with nephrostomy, and 44% of those patients needed no other treatment. Internal stenting of ureteral injuries without open surgery has also been successful.

If the ureteral injury cannot be managed with endoscopic techniques, or if it is not discovered at the time of injury, the management depends on four considerations: site of injury, time of recognition, associated injuries, and patient condition.[71] Types of ureteral trauma are contusion, partial laceration, complete laceration, crush injuries, and avulsions.

The management of contusions is simple. Contusions are discovered during surgical exploration and do not need intervention, unless necrosis is possible, and in these cases an internal stent and periureteral drain should be placed. Partial lacerations of the ureter can be repaired primarily, or they may be stented internally depending on their severity. Management of minor ureteral injuries is not affected by the location on the ureter.

The management of complete lacerations, avulsions, or crush injuries depends on the amount of ureter lost and the location along the ureter. If there is adequate healthy ureteral length, a primary ureteroureterostomy may be performed after the wound is débrided (Fig. 55-9). If there is insufficient healthy ureter present to allow primary reanastomosis in a

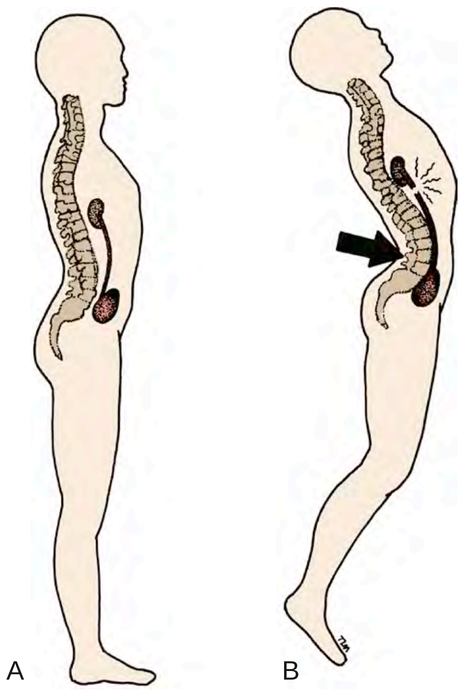

Figure 55-8 **A** and **B,** Mechanism of blunt injury leading to disruption of the ureter at the ureteropelvic junction in children. Children are thought to be so flexible that a blow to the back can result in acute hyperextension of the lumbar vertebral column. This hyperextension rapidly stretches the ureter between the kidney and the bladder, and disrupts the ureteropelvic junction. (From Gillenwater JY. *Adult and Pediatric Urology.* St Louis: Mosby-Year Book; 1996.)

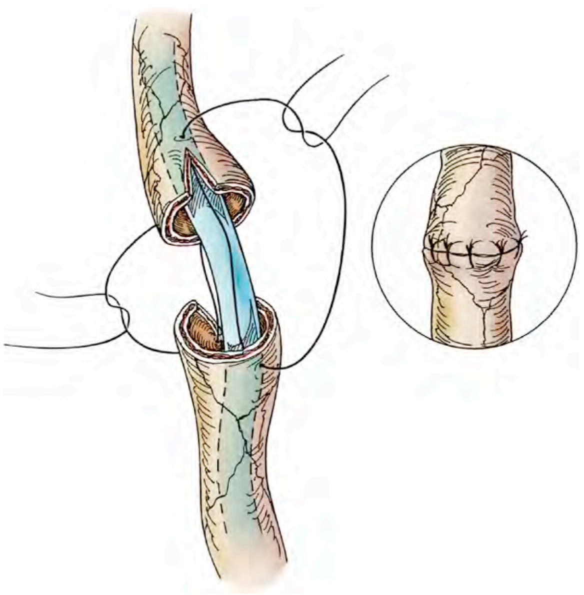

Figure 55-9 Repair of ureteral injury by ureteroureterostomy. The injured ureter is débrided and either spatulated or cut diagonally to create a longer anastomosis and to prevent stricturing. *Inset,* The ureteral ends are sutured together, ensuring that the anastomosis is not under tension and that adequate internal stenting and external drainage are provided. (From Armenakas NA. Ureteral trauma: surgical repair. *Atlas Urol Clin North Am.* 1998;6:79.)

distal ureteral injury, a psoas bladder hitch, Boari flap, or nephropexy may be helpful to make a ureteroneocystotomy possible (Fig. 55-10). Internal stenting and external draining is necessary in repair of all significant ureteral injuries. If the injury is to the proximal ureter or midureter, transureteroureterostomy, autotransplantation, or ureteral replacement with bowel or appendix are reasonable options.[98,99] If the patient's general condition does not allow immediate repair, a temporary ureterostomy and delayed reconstruction is another option that provides good drainage without tubes. Avulsion injuries of the ureteropelvic junction may be managed with a primary reanastomosis to the ureter if possible, and with a ureterocalycostomy if insufficient ureteral length is a problem.[75,100]

BLADDER INJURIES

The bladder is the largest organ in the urinary tract when it is full of urine. It is well protected in adults because it lies within the confines of the bony pelvis. The rigid pelvic ring and the rectus abdominis muscle guard it. The bladder occupies a less protected position in infants and children; it is a more abdominal organ and lies exposed above the pubis. The abdominal wall in children offers less protection because the rectus is less developed. There is also less pelvic and abdominal fat surrounding the bladder to cushion the bladder in trauma.

The exposed position of the bladder in children makes it more susceptible to blunt trauma when the bladder is full. This type of injury has been seen most often in motor vehicle accidents when the child is wearing a lap seat belt. Even with this relatively exposed position, the bladder is seldom injured from suprapubic trauma and without a significant pelvic fracture. In a review of 95 children with seat belt ecchymosis owing to trauma, only 3 had significant bladder injuries.[101]

The most common mechanism of significant bladder injury is blunt trauma. In a review of 111 adult bladder injuries, Corriere and Sandler[102] found that 86% were caused by blunt trauma, and 90% of those were the result of motor vehicle accidents. Most bladder injuries are associated with pelvic fractures in adults. Although bladder rupture is almost always associated with pelvic fracture, it is not true that most pelvic fractures lead to bladder injury. Only 10% of patients who sustain pelvic fractures have an associated bladder injury. Several studies analyzed the location and site of pelvic fracture and the relative risk of bladder injury.[103,104] Bladder injuries are more likely in patients who have multiple pelvic fractures, including a widened symphysis pubis and sacroiliac joint and fractures of the sacrum, iliac, and pubic rami. In their review of bladder ruptures, Sivit and colleagues[101] identified 7 children, and only 4, or 57%, had pelvic fractures compared with 89% in adults. This increased incidence of bladder rupture in the absence of pelvic fracture is the result of the more exposed position of the bladder above the pelvic ring in children.

The hallmark signs of bladder injury are suprapubic pain and tenderness, inability to urinate, and gross hematuria. All patients with bladder injury have significant microhematuria, and gross hematuria occurs in 95%. Of patients with the findings of pelvic fracture and gross hematuria, 45% have bladder rupture.[105] Bladder injuries seldom occur in isolation and are most often associated with multiple organ injuries, such as closed head trauma, other solid organ injuries, and severe hemorrhage. This accounts for the high mortality of 20% to 40% in patients with bladder rupture.[106]

The diagnosis of bladder injuries can be difficult and relies on filling the bladder retrograde through a catheter with contrast fluid and imaging with either standard radiographs or CT scans. The bladder should be imaged when fully distended

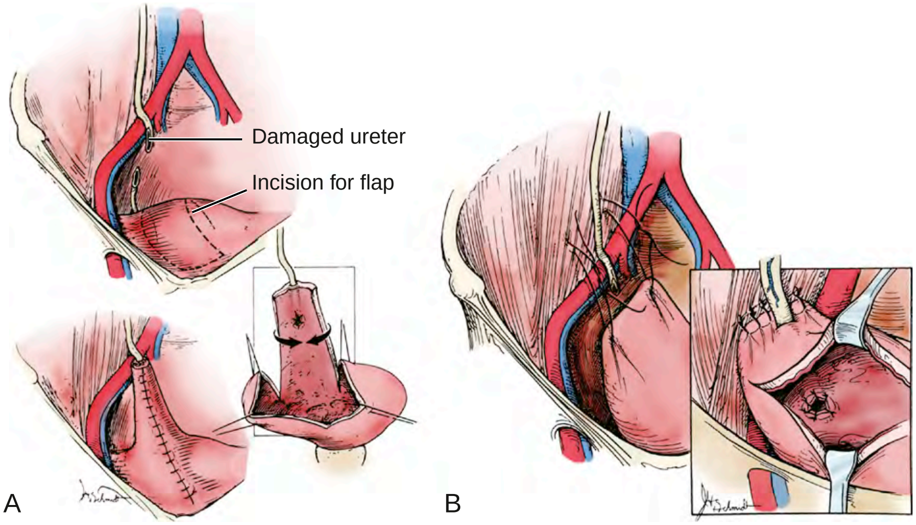

Figure 55-10 Methods of reconstruction when the distal ureter is lost. **A,** A modified Boari flap may be created by tabularizing a wide-based flap of bladder and rotating it toward the shortened ureter. A standard ureteral reimplant may be performed into the flap. **B,** The bladder may be moved closer to the ureter by shifting its position in the pelvis to the injured side and sewing it to the psoas muscle with a psoas bladder hitch. A ureteral reimplant may be performed with the shortened ureter. (From Guerriero WG. *Urologic Injuries.* East Norwalk, CT: Appleton & Lange; 1984.)

and after drainage. CT scanning of the bladder even with a clamped Foley catheter, if filled with contrast fluid excreted from the kidneys, is unreliable because the bladder is not forcibly distended. Spiral CT scanning has not provided more accuracy unless the bladder is filled in a retrograde manner.[107]

In a series of 1500 consecutive children with blunt abdominal trauma with a CT technique that included a delay of 20 to 30 minutes between intravenous injection of contrast material and scanning of the pelvis with the catheter clamped, Sivit and colleagues[101] diagnosed seven ruptured bladders and discovered no clinically apparent false-negatives. McAleer and coworkers[2] identified four children with traumatic bladder ruptures, and found one who had a delayed diagnosis because of multiple CT scans of the pelvis without retrograde bladder filling leading to false-negative findings. Even spiral CT is less accurate than retrograde cystography in diagnosing traumatic bladder rupture.[107] Despite advances in imaging techniques, the bladder must be filled to capacity to diagnose bladder injury accurately. In a review of 492 patients, the technique of filling the bladder with dilute contrast fluid before abdominal or pelvic CT scan for blunt trauma was found to have a sensitivity and specificity of 95% to 100%, and is equivalent to conventional cystography.[108]

Blunt injury to the bladder is categorized as either a contusion or a rupture. Bladder contusion is described as damage to the bladder mucosa or muscle without loss of bladder wall continuity or extravasation of urine. Most contusions manifest with hematuria, and the diagnosis depends on a thickened or irregular appearance of the bladder wall on imaging. Contusions account for one third of all bladder injuries and are treated with catheter drainage alone. The catheter is left in place until gross hematuria clears in most cases. It is unnecessary to image the bladder after the catheter is removed if the patient voids normally.

Bladder ruptures are described as either intraperitoneal or extraperitoneal, and differ in the site of injury, mechanism of injury, and treatment (Fig. 55-11). Intraperitoneal bladder rupture is more common in children because of the more exposed position of the bladder. The filled bladder is struck, and the acute increase in pressure caused by the trauma against the closed bladder neck causes the bladder to rupture at its weakest and most mobile point, the dome. The dome of the bladder is covered only by peritoneum, and a forceful tear in this area results in a communication with the peritoneal cavity. The diagnosis is made when the cystogram reveals contrast fluid within the peritoneal cavity classically outlining loops of bowel. These injuries account for one third of all bladder ruptures (Fig. 55-12).

Intraperitoneal bladder rupture often produces abnormal serum chemistries, including potassium, sodium, nitrogen, and creatinine. In a series of 22 children treated for traumatic bladder rupture, 44% were diagnosed immediately, and 56% had delayed diagnosis after 24 hours.[109] Of these children, 56% had intraperitoneal and 44% had extraperitoneal bladder rupture. Patients with intraperitoneal bladder ruptures and late presentation had increased serum levels of blood urea nitrogen, creatinine, and potassium. They had low levels of serum sodium. Patients with intraperitoneal bladder ruptures who presented early had increased creatinine and potassium. Patients with extraperitoneal ruptures had normal serum chemistries.

The accepted management of intraperitoneal bladder rupture is open surgical exploration and primary repair. This is considered an urgent procedure and includes irrigation of the peritoneal cavity. The peritoneal cavity is not drained, but the bladder is drained with either a suprapubic tube or a urethral catheter. Historically, suprapubic tube drainage has been the standard of care when the bladder is repaired from either blunt or penetrating injury, but more recent data have indicated that urethral catheters provide equally effective drainage and fewer complications resulting in shorter periods of diversion.[110,111] Several cases of intraperitoneal bladder rupture successfully repaired with laparoscopic techniques have been reported.[112,113] Rarely, intraperitoneal bladder ruptures have been treated with a urethral catheter alone.[114,115] After 7 to 10 days, the bladder is studied again with a cystogram to ensure healing, and the catheter is removed.

The second type of bladder rupture is extraperitoneal, and it occurs in the lower half of the bladder and is almost exclusively associated with pelvic fractures. With disruption

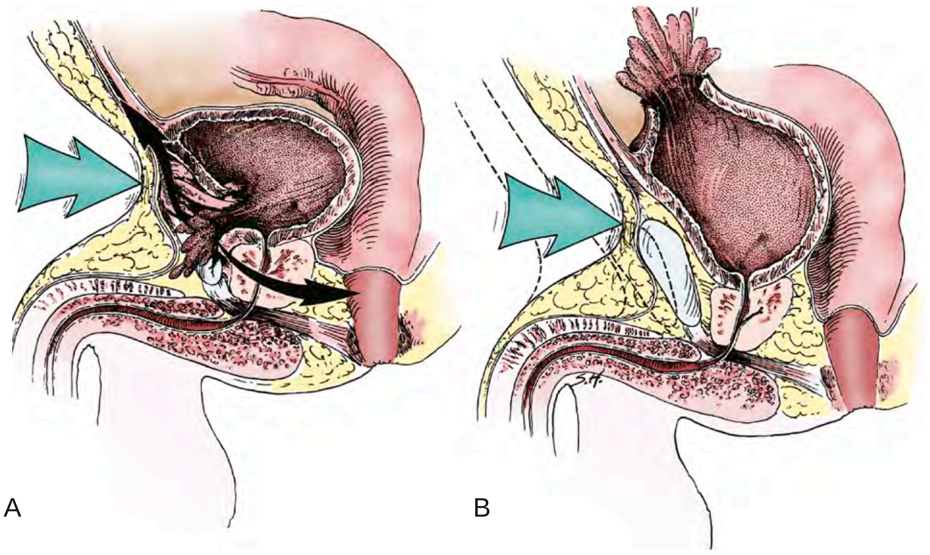

Figure 55-11 Mechanisms of blunt bladder injury. **A,** Extraperitoneal bladder injuries occur most often with pelvic fractures. The distortion of the bony pelvis and, in some cases, perforation of the bladder with bone fragments tear the lower bladder. **B,** Intraperitoneal bladder ruptures usually occur when blunt force is applied directly to the distended bladder. The bladder ruptures at the dome, resulting in a simultaneous tear of the overlying peritoneum and intraperitoneal urine extravasation. (**A** and **B,** From Walsh PC, Retik AB, Stamey TA, Vaughan ED Jr, eds. *Campbell's Urology.* 5th ed. Philadelphia: Saunders; 1986.)

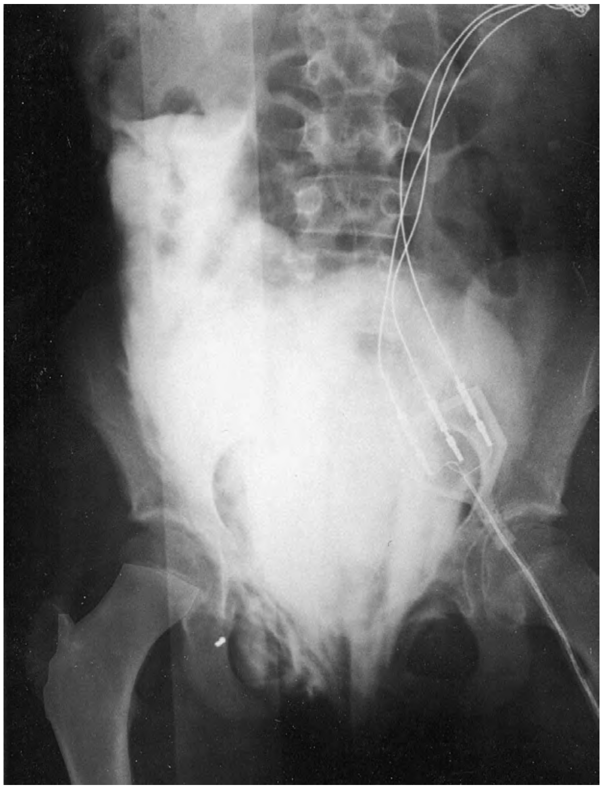

Figure 55-12 A 9-year-old boy sustained intraperitoneal rupture of the bladder as a passenger in a motor vehicle accident. The bladder was repaired primarily. (From King LR. *Urologic Surgery in Infants and Children.* Philadelphia: Saunders; 1998:277.)

of the bony pelvic ring, the bladder is torn on the lateral inferior wall and may be lacerated or penetrated with bone fragments. The cystogram reveals extravasation of contrast material into the perivesical soft tissues in a typical flame pattern, but the contrast material is confined to the pelvis. Almost all patients with extraperitoneal bladder ruptures are treated nonoperatively with urethral catheter drainage for 7 to 10 days.[116] More complicated injuries may necessitate exploration, débridement of nonviable tissue, repair, and extravesical drainage. If there are bone fragments noted within the bladder, they must be removed, and the bladder must be repaired and drained.

Significant complications of bladder rupture can occur even with conservative therapy. In a series of 29 patients with bladder rupture treated with a urethral catheter alone, 85% healed without surgery, but 3 patients required a prolonged period to heal, and 17% had complications. One patient had recurrent bladder calculi, two patients developed vesicocutaneous fistulas, one patient had persistent extravasation with sepsis, and one patient developed an infected pelvic hematoma and died.[117] Complications occur when bladder drainage is not maintained, and persistent extravasation occurs. Use of broad-spectrum antibiotics helps avoid the serious complications of infection.

In a review of 417 traumatic bladder injuries, penetrating trauma constituted only 5.5%.[51] Gunshot wounds are the most common type of penetrating bladder injury followed by stabbings. Associated traumatic injuries are common, and the mortality is 12% to 22% secondary to those extraurinary injuries. Injuries to the rectosigmoid, small bowel, and iliac vessels are the most common associated injuries.

Penetrating bladder trauma requires surgical exploration and repair. In the case of gunshot wounds, débridement of nonviable bladder tissue surrounding the wound is usually necessary. The perivesical space and the bladder should be drained. Pelvic hematoma and fecal contamination from rectal injuries may complicate these wounds. Simultaneous diversion of the bowel is common in multisystem complicated injury.

URETHRAL INJURIES

Because of its shape, elasticity, and location, the urethra is seldom injured from trauma. The urethra begins at the bladder neck and extends to the external urinary meatus. The bones

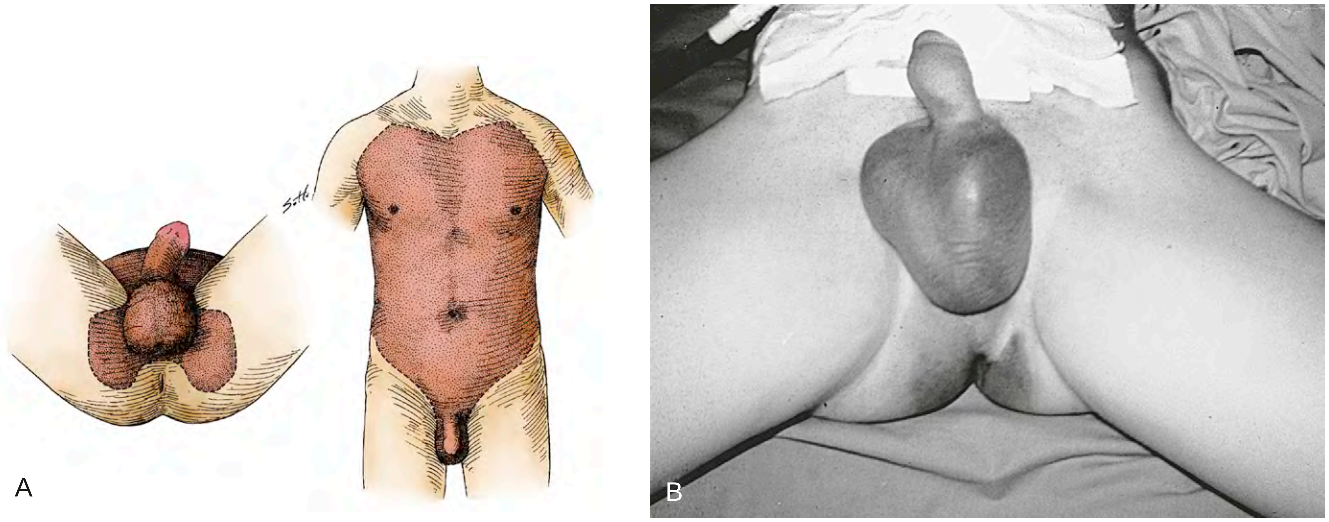

Figure 55-13 **A,** Colles fascial attachments, which define the limits of extravasation of urine or blood from a urethral injury. **B,** A patient with a perineal butterfly hematoma with bleeding limited by Colles fascia. (**A,** From Walsh PC, Retik AB, Stamey TA, Vaughan ED Jr, eds. *Campbell's Urology.* 5th ed. Philadelphia: Saunders; 1986; **B,** from King LR. *Urologic Surgery in Infants and Children.* Philadelphia: Saunders; 1998.)

of the pelvis and extensive soft tissue of the perineum protect the entire urethra with the exception of the penile urethra. Injuries of the penile urethra are discussed in association with genital injuries. Injuries to the female urethra are rare and are discussed separately.

Posterior Urethral Injuries

The male posterior urethra begins at the bladder neck and includes the prostatic urethra, the membranous urethra, and the bulbous urethra. The urethra is fixed in the bony pelvis as it passes through the muscles of the pelvic floor. The bladder and prostatic urethra sit above the pelvic floor, and the bulbous urethra lies below the floor and outside of the pelvis. The membranous urethra is the portion that passes through the pelvic floor and is fixed to the bony ring. In adults, the prostate supports the prostatic urethra and protects it from injury. In children, the prostate is poorly developed and offers little protection. Injuries to the posterior urethra are almost always secondary to fractures of the pelvis and the result of severe blunt trauma.

When fractured by severe trauma, the pelvic ring that supports the pelvic floor is disrupted, and shear forces may pull the prostate and bladder violently away from the fixed membranous urethra. The membranous urethra may be lacerated or totally disrupted. The severity of the pelvic injury may vary, but the site of associated urethral injury is constant at the membranous urethra. Urethral injuries secondary to pelvic fracture are consistently associated with pubic arch (straddle) fractures combined with diastasis of the sacroiliac joint.[118] This type of pelvic fracture has a 24 times greater risk of injuring the urethra than other pelvic fractures. Ten percent of pelvic fractures result in urethral injury, and 83% of these are complete urethral disruptions. Ninety percent of urethral injuries are the result of motor vehicle accidents, and falls, industrial accidents, and sporting accidents make up the rest.[119]

Because of the different pelvic anatomy, children sustain posterior urethral injuries not found in adults.[120] The immature and thin prostate adds little support to the posterior urethra, and the puboprostatic ligaments are weak. The lack of support in the prostatic urethra allows different types of laceration secondary to trauma. Children sustain the classic membranous urethral disruptions that are common in adults, but they also can have lacerations of the prostatic urethra itself and disruption of the urethra at the bladder neck. In a series of 24 children with posterior urethral disruptions, 67% had classic membranous urethral injury, 17% had urethral lacerations above the prostate, and 17% had lacerations to the prostatic urethra.[121] Supraprostatic and prostatic urethral lacerations are extremely rare in adults.

Urethral trauma produces considerable bleeding into the soft tissues of the pelvis and perineum. Injuries to the membranous urethra cause perivesical bleeding and may result in a large pelvic hematoma. The patient usually cannot void, and urine extravasates into the soft tissue. The hematoma and urinoma may force the bladder and proximal urethra away from the pelvic floor and produce a gap of several centimeters between the severed urethra. If the bladder neck is intact, the bladder may retain urine and become extremely distended. If the bladder neck is injured, urine usually leaks out continuously, and the bladder appears empty.

Bulbous Urethral Injuries

The classic injury to the bulbous urethra is a result of straddle trauma. The patient falls onto a fixed object with one leg on either side. Straddle injuries occur with bicycles, playground equipment, and fences. Assault with kicking resulting in trauma to the perineum can produce the same results. Straddle injuries occur when the urethra and surrounding corpus spongiosum are crushed against the pubic rami by force from the perineum.

Most straddle injuries do not lead to extravasation of urine because the urethra is crushed and not lacerated. Also, there are no forces that displace or retract the urethra apart. There is usually severe bleeding into the perineum because the blood is limited from entering the pelvis by the pelvic floor. The bleeding produces a classic butterfly pattern within the perineum within the limits of Colles fascia (Fig. 55-13). If the patient cannot void after a straddle injury, it is usually due to edema and compression of the urethra by hematoma. The main complication of blunt straddle injuries to the bulbous urethra is urethral stricture. Most of these strictures require open surgical repair, and the long-term success rate is 95% in a series of 78 patients presented by Park and McAninch.[122]

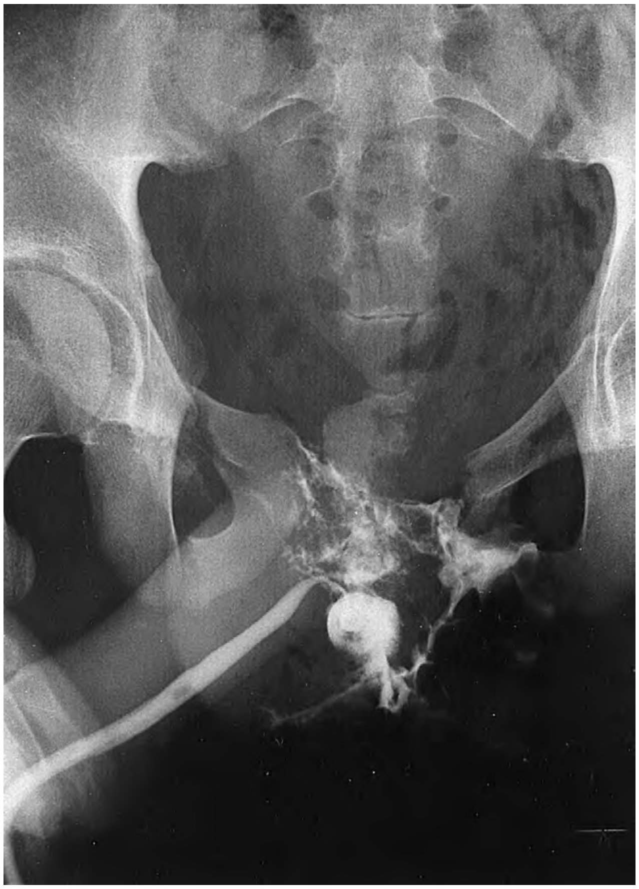

Figure 55-14 Retrograde urethrogram shows a prostatomembranous urethral injury. There are bilateral pubic arch fractures. The contrast material extravasates into the soft tissues of the pelvis.

Evaluation and Management of Urethral Injuries

Any patient who has sustained a pelvic fracture or significant trauma to the perineum should be suspected to have a urethral injury until studies indicate otherwise. Signs of urethral injury include blood at the meatus, gross hematuria, severe pain on voiding, and inability to void. Perineal edema or hematoma involving the scrotum is also a sign of urethral injury. Any patient suspected to have a urethral injury should undergo a rectal examination to determine the position and fixation of the prostate. In membranous urethral injuries, the prostate and bladder may be displaced up out of the pelvis, and this is apparent on rectal examination.

Almost without exception patients who are suspected to have urethral injuries and pelvic fractures have been involved in severe trauma to multiple organ systems.[123] Because many of these patients are unstable, and the extent of their other injuries is still undefined, the urologist's initial responsibility is to provide a way to drain and monitor urine output. If the patient has voided, and the rectal and pelvic examination does not suggest urethral injury, a urethral catheter may be placed immediately. If the catheter does not pass easily, radiographs of the urethra should be performed immediately. If other injuries necessitate that the patient be taken to the operating room, the urologist may place a suprapubic tube or use a cystoscope to place a urethral catheter. If the patient is unstable and is not being taken to the operating room, a percutaneous suprapubic tube may be placed in the emergency department, provided that the bladder is full.

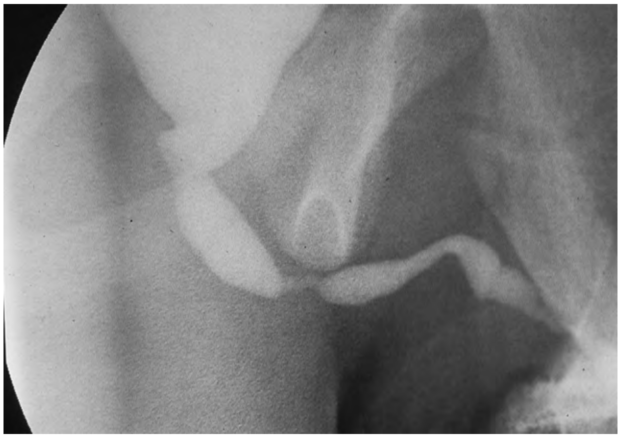

Figure 55-15 Voiding cystourethrogram shows a bulbous urethral stricture in a 6-year-old boy resulting from a straddle injury that occurred months before. The relationship between the stricture and the pubic bone is easily visible.

Radiographic evaluation of the urethra requires a retrograde urethrogram (Fig. 55-14). This study may be performed in the emergency department if necessary to save time or to avoid unnecessary movement of the injured patient. The urologist pulls the patient's penis upright to straighten the urethra, and a catheter is placed in the distal urethra to allow injection of contrast fluid under pressure into the lumen. The radiograph should include views of the entire urethra including the bladder neck, and it is helpful either to place the patient in the oblique position or to rotate the imaging equipment to provide an oblique view. If the study shows continuity of the urethra, a Foley catheter may be placed into the bladder under radiographic control. If a catheter has been placed previously into the bladder, and urethral trauma is in question, the catheter should not be removed. A small feeding tube can be placed in the distal urethra along the bladder catheter, and contrast material can be injected to outline the urethra for injury.

The management of posterior urethral injuries differs from the management of injuries of the bulbous urethra because of associated severe injuries and the amount of tissue damage resulting from trauma to the posterior urethra. Bulbous urethral or straddle injuries are often uncomplicated by associated injuries to other systems and cause minor tissue damage. The management of bulbous urethral injuries is simple and involves either observation or urethral catheter drainage to prevent urethral bleeding or painful voiding. Often the patient has minor dysuria and transient hematuria. Straddle injuries often resolve without the patient being evaluated by a physician and come to light later when a stricture develops at the injury site (Fig. 55-15).

The initial management of injuries to the posterior urethra is not so straightforward and produces considerable ongoing controversy. The main feature of the debate is whether performing a primary realignment of the urethra with a catheter provides better long-term results than simple suprapubic drainage and later reconstruction of the urethra. The measures of success in injuries of the posterior urethra are the ability to provide a stricture-free urethra, while avoiding the complications of urinary incontinence and impotence. Historically, immediate surgical repair of these injuries resulted in significant bleeding and high rates of incontinence (21%) and impotence (56%).[124] Because of these poor results, the concept of suprapubic catheter drainage and late urethral reconstruction was adopted. Immediate urethral repair should be avoided except in rare injuries involving the bladder neck.

The immediate result of suprapubic drainage alone is stricture formation of the injured portion of the posterior urethra in 97% of cases.[102] The occasional patient who does not form a stricture probably represents an unrecognized partial urethral injury that healed spontaneously. There are various methods to repair the resulting stricture, but the most common is to excise the fibrotic scarred urethra and spongiosum and to perform a primary reanastomosis either through the perineum or through a transpubic approach. Success rates of this delayed urethral repair include restricture rates of 11% to 30% in modern series.[123,125] These recurrent strictures are for the most part minor in severity and respond to dilation or endoscopic urethrotomy. Continence rates after surgery are 90% to 95%; some patients have mild stress incontinence, and some have neuropathic bladders secondary to associated pelvic nerve trauma. Impotence occurs in 62% to 68%.[103-105]

Experience with children has been similar, but is much more limited. Koraitim[126] reported on 68 boys with posterior urethral injuries secondary to fractured pelvis and had a success rate of greater than 90% with delayed repair. Failures were defined as any patient who required repeated treatment of strictures or incontinence. Boone and associates[121] reported on 16 children with posterior urethral injuries, 9 of whom were treated with suprapubic drainage and delayed repair. Strictures and impotence were complications in 67% of boys, but all were continent. Zhang and coworkers[127] reported on 24 boys with posterior urethral strictures treated in various approaches and had the best results (90% success) using a transperineal–inferior pubic approach.

Other options for urethral repair after initial management with suprapubic urinary drainage include patch urethroplasty with skin and endoscopic "core through" optical urethrotomy.[128,129] Results of either method have been inferior to excision of scar and "primary" reanastomosis in terms of providing a stricture-free urethra. Proponents of endoscopic management cite the advantages of minimal morbidity and hospitalization, but the unfavorable restricture rate of 65% should also be considered.

The other viable option to initial suprapubic urinary drainage and delayed repair is primary realignment of the urethra over a catheter. The most common technique is to perform an open cystostomy and to pass a sound or catheter from the bladder neck or from the meatus through the injured segment. A larger catheter is placed and left in position to provide urinary drainage, to align the urethral ends, and in some hands to provide gentle traction to help bring the ends back into opposition.

Elliott and Barrett[130] reported on 57 patients with urethral disruption managed by primary urethral realignment within 6 hours of injury. Incontinence was a complication in 3.7%; strictures occurred in 68%, but of these 64% required either dilation only or no treatment. Impotence occurred in 20%. Kotkin and Koch[131] reported on 20 patients managed with initial realignment and compared them with 12 patients treated with delayed repair with similar results of 83% continence and 76% potency in the realignment group. Mouraviev and colleagues[132] reported a series of 57 patients treated with early realignments compared with 39 patients treated with suprapubic tube drainage, and found strictures in 49% of early realignments in contrast to 100% of the diverted group. It is now generally accepted that the complications of incontinence and impotence are a result of the initial trauma, rather than due to surgical repair. Only immediate surgical repair seems to have a significant negative effect on outcome and should be avoided.

The experience of primary urethral realignment in children is limited, but Avanoglu and associates[133] reported 14 children who underwent primary catheter realignment with 29% stricture rate and only 7% incontinence. These authors also found that continence and stricture rates depended most on the type and location of the urethral injury. They advised using mild traction on the urethral catheter to bring the torn urethral ends back into opposition. Excessive traction has produced ischemic injury to the bladder neck in adults.[134]

Injuries to the prostatic urethra and bladder neck are more complicated than membranous urethral injuries and are more likely to produce incontinence. Boone and associates[121] reported four children with prostatic urethral tears and four with urethral injuries above the prostate. These eight patients underwent primary repair with poor results; 75% had severe strictures, and the same percentage was impotent. Twenty-five percent were incontinent. Avanoglu[133] presented 17 children with prostatic or supraprostatic urethral injuries repaired by various methods that produced a 41% stricture rate and a 41% rate of incontinence. Most authors suggest that injuries of the bladder neck should be repaired primarily, but that initial repair of the prostatic urethra may cause more damage to the nerves and continence mechanism and should be avoided.

Current recommendations for the management of posterior urethral injuries of the prostatic and membranous urethra depend on the stability of the child from the accident. If the patient is unstable and in a life-threatening situation, a suprapubic tube should be placed in the emergency department for drainage of urine until the patient is stable. If the patient is going to the operating room for other treatment, or if the patient is stable and was found to have a wide separation of completely severed urethral ends, primary realignment of the urethra should be performed with catheters, sounds, or use of endoscopy.[135,136] The catheter should be left in the urethra for 4 to 8 weeks; simultaneous suprapubic tube drainage may be helpful. If the patient has an incomplete urethral disruption, or if the urethral ends are not widely separated and if the urethra cannot be easily realigned with a catheter, suprapubic tube drainage alone is an acceptable alternative with good results after delayed urethral repair. Repair of the resulting stricture should be delayed for 4 to 6 months.

Traumatic Injuries to the Female Urethra

Isolated injuries to the female urethra are quite rare because of three factors: (1) its short length, (2) its protected location, and (3) its considerable mobility compared with the male urethra.[137,138] Injuries to the urethra are due to two types of trauma—severe pelvic fractures and extensive soft tissue injuries to the vulva, vagina, and urethra. The exact incidence of female urethral trauma is unknown, but Orkin[139] reviewed 2000 cases of pelvic fracture in girls and women and found a 6% incidence of urethral injury. Most reports of urethral injury have been in girls, suggesting that women are either less vulnerable or tend to die from the associated injuries that lead to urethral trauma.[140] The high estrogen levels that thicken and increase the distensibility of the vulvar tissue and protect the genitals from injury in postpubertal girls and women may also protect the urethra in trauma.[141]

Urethral injuries in the female may occur as either transverse disruption or transection, usually at the bladder neck, or as longitudinal tears that extend down through the bladder neck into the urethra.[142,143] The entire urethra may be lost from avulsion and infarction.[144] The most common cause of urethral trauma is motor vehicle accident leading to severe pelvic fractures. When the pubis is disrupted violently leading to an acute diastasis of the symphysis, the urethra is torn by its soft tissue attachments. The vagina is usually injured at the same time, and 80% of patients with urethral injury present with vaginal bleeding.[117] Labial edema and hematoma also usually accompany urethral injury. Studies of long-term outcome in these patients reveal moderate or severe lower urinary tract symptoms in 43% and sexual dysfunction in 38% at a mean of 7 years.[145]

Indications to investigate a urethral injury in a girl include pelvic fracture, difficulty to place a urethral catheter, vaginal bleeding, or anuria after catheter placement. Despite the fact that concurrent bladder ruptures occur in 66% of female urethral injuries, static cystograms may miss a urethral injury.[146] A voiding study is necessary to rule out urethral injury.

Management of urethral injuries in girls depends on the degree of injury and the ability to place a urethral catheter. If the bladder neck is intact, and a catheter can be placed through the urethra into the bladder, the injury may be treated without initial surgery. If a catheter cannot be placed from the meatus, the same options are available as in boys. A suprapubic tube may be placed, and the urethral injury may be left untouched and allowed to heal primarily. As a second option, a catheter may be placed from above using either sounds or endoscopy, and leaving the catheter to align the damaged urethra. If the injury traverses the bladder neck or communicates with a vaginal laceration threatening continence, a primary surgical repair is indicated when the patient's condition allows. Long-term catheter drainage and stenting is essential.

REFERENCES

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PART X

RECONSTRUCTION AND SURGERY FOR INCONTINENCE

SECTION 1

BLADDER RECONSTRUCTION AND SUBSTITUTION

CHAPTER 56

INCONTINENT AND CONTINENT URINARY DIVERSION

Peter D. Metcalfe and Mark P. Cain

Urinary diversion is defined as the surgical diversion of urine from the intact urinary tract, and can be classified as either incontinent or continent. Incontinent diversion allows for the free flow of urine outside of the body; urine can be collected into either a diaper or an external ostomy device. With continent urinary diversion, the urinary reservoir is emptied by clean intermittent catheterization (CIC); this allows for urinary dryness or "continence." Classically, a reservoir made entirely of gastrointestinal segments (i.e., with no native bladder) is referred to as a continent urinary reservoir (CUR). This procedure is less commonly used in pediatric patients, however, because most diagnoses that require urinary reconstruction (e.g., spinal dysraphism, exstrophy, posterior urethral valves) do not necessitate cystectomy. In this group of patients, bladder augmentation with preservation of the native bladder is the procedure of choice because it avoids the added complications associated with reimplanting the ureters into a bowel segment.

Historically, urinary diversion was employed to protect the kidneys from the deleterious effects of increased bladder pressure, but today it is increasingly used to achieve urinary continence. First-line treatment is always conservative, with CIC and anticholinergic agents. Indication for surgical therapy is noncompliance or failure of medical management, which may manifest as recurrent urinary tract infection (UTI), hydronephrosis, or de novo vesicoureteral reflux. A congenitally abnormal bladder requires urodynamic investigation; this stratifies the high-risk urinary tract and dictates the necessary interventions required to attain continence.[1] The development of surgical techniques to allow storage of urine at safe pressures has reduced the use of permanent incontinent urinary diversion, but this still retains an invaluable role.

INCONTINENT URINARY DIVERSION

Incontinent urinary diversion is an extremely valuable tool for the protection of the upper urinary tract because it is a very effective means of reducing elevated intravesical and intrarenal storage pressures. There are numerous means of achieving this, and complexity ranges from a temporary urethral catheter to a permanent incontinent ileovesicostomy.

Urethral Catheter

The simplest and most frequently used incontinent urinary diversion is the urethral catheter. This can be used for the immediate drainage of bladder outlet obstruction (e.g., posterior urethral valves, ureterocele), for instillation of a contrast agent for radiographic study, and for the accurate recording of urine output in a seriously ill child. We prefer to catheterize neonates with a 5F or 8F feeding tube; however, care must be taken not to insert too much tubing because it may become knotted inside the bladder and become difficult to remove.[2] In an older child who requires bladder drainage, a 6F or 8F balloon (Foley) catheter is a reasonable alternative. Intermittent catheterization is another option for children with urinary retention and has proved to be safe even in neonates. Complications of urethral catheters in children are usually related to improper placement or prolonged use, and include urethral injury, urethritis or meatitis, UTI, urethral stricture, urethral erosion, and bladder stones.

Although usually very simple to insert, urethral catheterization in patients with posterior urethral valves can be difficult if the urethra has become elongated and dilated with an elevated bladder neck. In this scenario, a coudé tip catheter may negotiate the bulbomembranous angle, or a small lacrimal duct probe can be used as a catheter guide. It is sometimes helpful to place a finger in the rectum because this elevates and straightens the prostatic urethra. With every complicated catheter placement, especially when associated with renal compromise, correct placement should be confirmed with ultrasound or fluoroscopy and the injection of contrast material.

Percutaneous Suprapubic Cystotomy

A suprapubic cystotomy tube can be an excellent means of short-term or long-term bladder drainage, especially when urethral access is impossible. Although general anesthesia is normally required in children, conscious sedation and local anesthesia may suffice. A full bladder is an absolute prerequisite, and can be ensured by initial placement of a small angiocatheter to localize and to fill the bladder. If the patient has had a previous suprapubic tube, the established track usually results in a safe re-entry point, especially if the bladder and tube were sutured to the posterior fascial wall at the time of initial placement.

These tubes are designed for temporary bladder drainage; long-term use has been associated with bladder wall thickening and contracture, UTI, bladder stones, and upper urinary tract dilation.[3,4] Permanent use can result in chronic bladder inflammation, increasing the risk of malignant degeneration and squamous cell carcinoma.[5]

Cutaneous Vesicostomy

Cutaneous vesicostomy is the most common form of incontinent urinary diversion in neonates and young children. This technique has limited use for older children and adults, however, because the bladder is much more difficult to mobilize and secure outside the pelvis. Neonates with bladder outlet obstruction (e.g., posterior urethral valves or a cloaca)[6] are occasionally too small to undergo definitive surgery, and a vesicostomy offers an excellent means of reducing intravesical pressure until a definitive reconstructive procedure is possible. Infants with a neuropathic bladder and unsafe storage pressures may require vesicostomy if the patient's caregivers are unwilling to perform CIC, or, despite maximal medical treatment, safe bladder pressures cannot be maintained. Very rarely, young infants with high-grade vesicoureteral reflux, hydronephrosis, and multiple breakthrough UTIs may also benefit from temporary vesicostomy to reduce bladder and renal pressures.[7,8]

Several studies have confirmed the effectiveness of a vesicostomy, with regards to either a reduction in upper tract dilation or improvement in renal function.[7-12] Reflux has been reported to improve significantly enough to decrease the need for ureteral tapering at reimplantation.[7,8] Although bacterial colonization of the open system is expected, symptomatic infections and urosepsis are uncommon.[10,11] A pressing contemporary argument against a vesicostomy, or any supravesical diversion, is the impact of preventing the congenitally abnormal bladder from undergoing the normal "cycle" of filling and emptying, and potentially resulting in a more diseased bladder in the long-term.[13-15] Several studies have shown good bladder function after closure of the vesicostomy, however.[8,16,17]

Although first described by Lapides and colleagues,[18] most contemporary surgeons employ the technique described by Blocksom[19] and Duckett[20] (Fig. 56-1). The Blocksom vesicostomy is fashioned through a small transverse incision halfway between the umbilicus and the pubis. A vertical incision may be used if future reconstruction is anticipated, minimizing excess cutaneous scar. The fascia is incised, and the peritoneum is mobilized superiorly off the dome of the bladder. The urachal remnant is divided, and the dome of the bladder is mobilized to reach the skin without tension. The fascia is secured to the bladder wall to form a 24F defect, and the mucosa is everted or sewn flush with the skin.

Complications of cutaneous vesicostomy include stomal stenosis, prolapse, peristomal dermatitis, and bladder calculi. The risk of prolapse is minimized by limited mobilization of the bladder, and securely suturing the dome of the bladder to the fascia of the anterior abdominal wall. Dermatitis is usually a result of a superficial fungal infection, and is effectively managed with a barrier cream or a topical antifungal. Bladder calculi may indicate poor drainage, probably secondary to stomal stenosis, and this should be addressed at the time of stone surgery.

Surgical closure of the vesicostomy is technically straightforward, but it cannot be performed without careful consideration and appropriate planning. Urodynamic evaluation must be performed with occlusion of the vesicostomy, in an attempt to predict vesical pressure after closure. If pressures remain elevated, consideration must be given to either simultaneous bladder augmentation at the time of vesicostomy closure or close observation with an understanding with the family that a second operation with augmentation of the bladder may be required. The surgeon and family must remain cognizant of the fact that closure may be deleterious to the child's health, and that caregivers would be responsible for an increased level of care.

Cutaneous Ureterostomy

Ureterostomy for temporary supravesical urinary diversion is rarely performed today because expertise in pediatric percutaneous radiologic and endourologic techniques has become available in most tertiary referral centers. Historically, ureterostomy was used to decompress an obstructed or infected upper pole,[21] and it is still considered an option in very small neonates.[22] Ureterostomy is also very effective for preservation of renal function where maximally effective upper tract drainage is required. Finally, supravesical diversion may be indicated in a patient with posterior urethral valves, whose renal function fails to improve after maximal bladder drainage, and there is suspicion of a ureterovesical junction obstruction.[23]

Temporary diversion is most commonly accomplished with a low loop ureterostomy because this is easily reversed. An end ureterostomy is most useful for an ectopic ureter because it eventually would require transection and ureteroneocystotomy for reconstruction. The resultant proximal decompression may facilitate subsequent reconstruction because ureteral tapering can be avoided in some cases. High diversion, at the level of the kidney, is performed through a flank incision and can be performed as a loop ureterostomy, Sober ureterostomy, or end ureterostomy. Similar to the cutaneous pyelostomy, these procedures are rarely performed today because subsequent reconstruction of the ureteropelvic junction can be very difficult. Contemporary practice in this scenario usually results in a percutaneous nephrostomy tube because this is less disruptive to the pelvis and its blood supply.

Percutaneous Nephrostomy Tube

Percutaneous nephrostomy tubes have evolved as an effective and safe means to achieve temporary upper urinary tract drainage.[24-26] Insertion is usually performed by a pediatric radiologist with ultrasound and fluoroscopic guidance, and is performed under local or general anesthesia.[27] It has been performed safely in infants weighing only 1200 g.[27] Serious

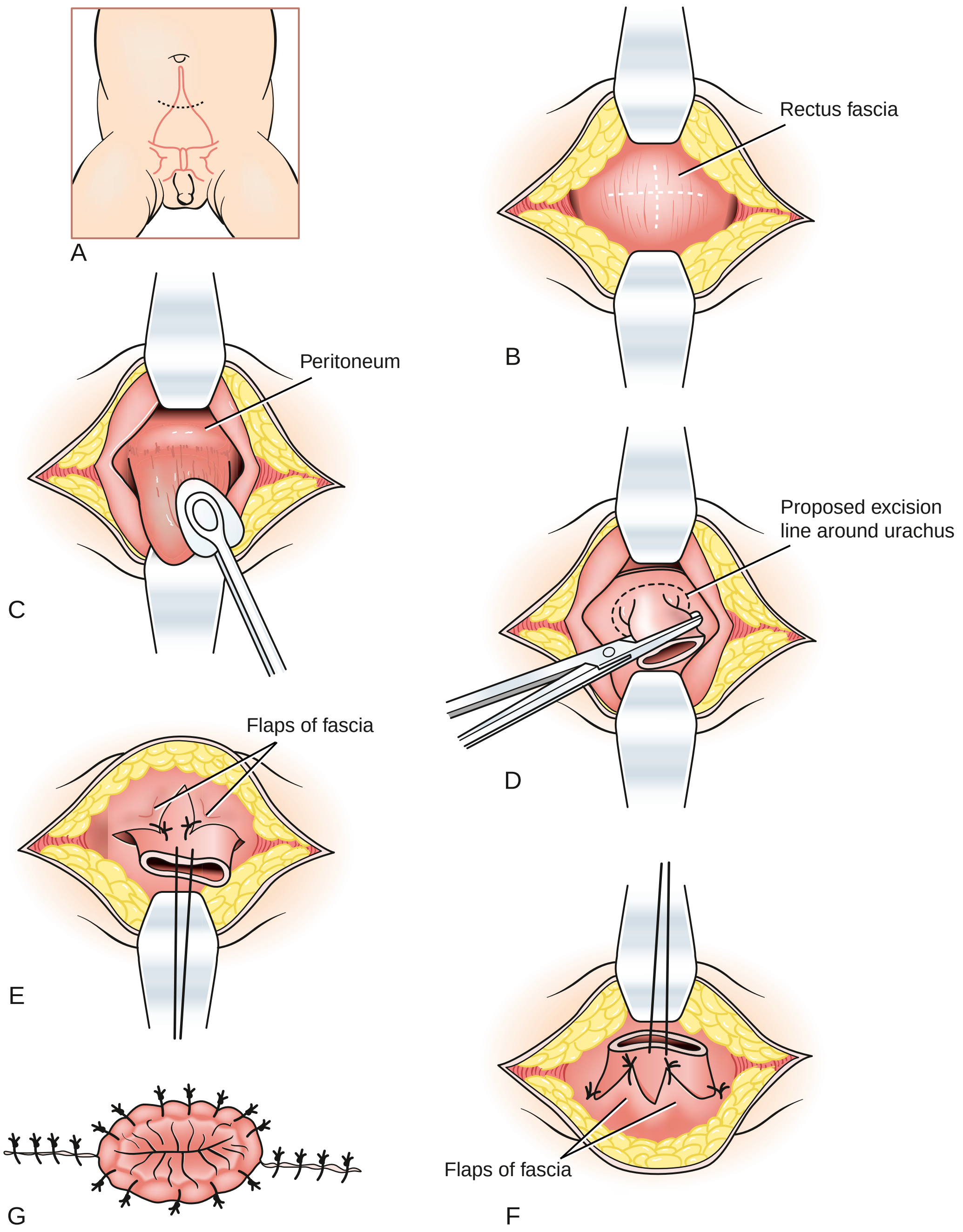

Figure 56-1 **A-G,** The Blocksom vesicostomy, showing the incision in the dome of the bladder, the fixation to the overlying fascia, and the everted stoma. (From Cain MP, Metcalfe PD, Rink RC. Urinary diversion. In: Docimo SG, Canning DA, Khoury AE, eds. *Clinical Pediatric Urology*. 5th ed. Boca Raton, FL: Informa Healthcare; 2007, Figure 57.2.)

complications are uncommon, but minor complications occur frequently and include hematuria, tube dislodgment, and bacterial colonization.[27] Percutaneous access can also be used for diagnostic radiographic studies (nephrostogram), for recording differential urine output,[26] or for an antegrade renal pressure perfusion (Whitaker test).

Ileal and Colon Conduits

The ileal conduit was first described by Zaayer in 1911 and popularized by Bricker in the 1950s as a form of diversion after cystectomy.[28,29] The ileal conduit was an important alternative procedure for urinary diversion in that era because the threat of profound metabolic derangements muted enthusiasm for the ureterosigmoidostomy.[28] Ileum is the most commonly used gastrointestinal segment for conduits, owing to the abundant supply, long mesentery, and ease of use. Colon conduits have the advantage of a reliable antireflux mechanism, however, by reimplanting the ureters into the taeniae coli (Fig. 56-2). Reflux has been reported in 58% of colon conduits, however.[30]

The most common postoperative surgical complications include stomal stenosis, stomal prolapse, and peristomal hernia. These are best prevented with careful surgical technique, with strict attention to perfusion of the bowel segment,

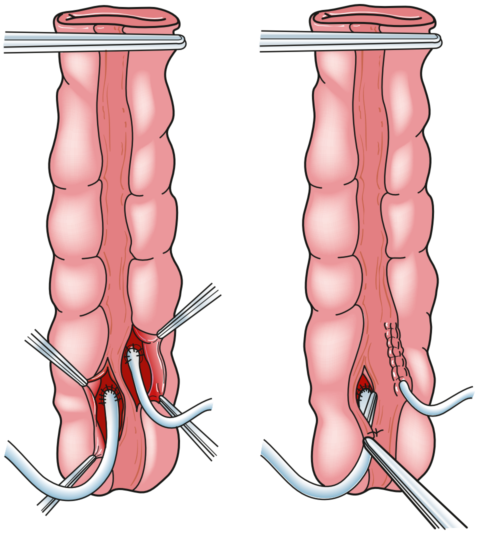

Figure 56-2 Nonrefluxing ureterocolonic anastomosis with ureters reimplanted within taeniae coli. (From Cain MP, Metcalfe PD, Rink RC. Urinary diversion. In: Docimo SG, Canning DA, Khoury AE, eds. *Clinical Pediatric Urology*. 5th ed. Boca Raton, FL: Informa Healthcare; 2007, Figure 57.7.)

creation of a straight and adequate caliber fascial window, and fixation of the conduit to the fascia. A protuberant rosebud stoma minimizes the risk of stenosis and enhances the fit of the stoma appliance, which reduces urinary leakage and peristomal dermatitis (Fig. 56-3).

The risk of upper tract deterioration is less of a concern in elderly patients, but is extremely relevant in pediatric patients. Ureteral anastomotic stricture occurs in 9% to 22%, and resultant deterioration of the upper tracts occurs in 26% to 48%.[30,31] Koch and associates[31] compared a cohort of myelomeningocele patients with ileal conduit diversion with another group managed with CIC. The ileal conduit group showed a significantly higher rate of renal deterioration, nephrolithiasis, and pyelonephritis, especially in patients with a dysfunctional ureterointestinal anastomosis.[31] Although minimal metabolic derangements were seen with conduits, these patients showed impaired linear growth, more spinal curvature, and more complications from orthopedic procedures.[31]

Incontinent Ileovesicostomy

The incontinent ileovesicostomy (ileal chimney) was reported by Schwartz and associates in 1994,[32] as a variation of the vesicostomy adapted for adults. Because the adult bladder frequently does not reach the abdominal wall, a segment of ileum can be anastomosed to the in situ bladder, and brought out as a urinary stoma (as per an ileal conduit). This procedure allows for a low-pressure system, the ability to use a urinary appliance, the avoidance of "diapering," and the avoidance of the inherent complications of the ureterointestinal anastomosis. Another advantage to the incontinent ileovesicostomy is flexibility regarding body habitus and position of ostomy because a significant length of ileum can be used.[33] Several series report excellent results with regard to preservation of renal function, incidence of UTI, urolithiasis, and stomal complications.[33-36]

Preoperative preparation is identical to the ileal conduit, with bowel preparation and selection of a stoma site. The bladder is bivalved in the coronal plane and anastomosed to the widely spatulated ileum. A rosebud stoma is fashioned at the predetermined site and with a large catheter in the stoma, and a suprapubic tube is placed to ensure maximal drainage and irrigation of mucus.

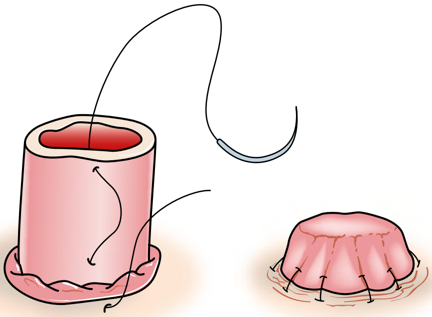

Figure 56-3 Eversion of stoma at the skin level creates a nipple effect that allows a snug-fitting appliance, decreasing the risk of peristomal problems. (From Cain MP, Metcalfe PD, Rink RC. Urinary diversion. In: Docimo SG, Canning DA, Khoury AE, eds. *Clinical Pediatric Urology*. 5th ed. Boca Raton, FL: Informa Healthcare; 2007, Figure 57.6.)

Postoperative complications secondary to an ileal conduit or chimney can be seen as intermediate in severity between a vesicostomy/ureterostomy and a CUR. The use of any intestinal segment predisposes the child to complications associated with a laparotomy (e.g., anastomotic leak, bowel obstruction) and effects from the loss of the segment (e.g., vitamin malabsorption, diarrhea). Intestinal mucus promotes bacterial colonization and calculus formation in the bladder.[30,37] Because of the nondependent drainage of the ileovesicostomy, daily bladder irrigation may be required to reduce complications from stagnant urine and mucus. Because the bowel retains its absorptive properties, metabolic acidosis is a possibility, but less likely than a continent diversion, owing to the decreased contact time with the bowel mucosa. Malignant degeneration is a concern whenever the gastrointestinal tract is used in the urinary tract, and although we are unaware of any report associated with an ileovesicostomy, the theoretical risk exists.[30,38-40]

CONTINENT URINARY DIVERSION

Many different types of continent urinary diversions have been developed to augment or replace the native lower urinary tract; these generally can be divided into two categories. A CUR completely replaces the bladder, whereas an intestinocystoplasty (bladder augmentation) uses the bladder in situ.

The original continent diversion was the ureterosigmoidostomy.[41] Although still used, it has fallen out of favor because of the high risk of electrolyte abnormalities and malignancy.[28,40,42-46] Most contemporary pediatric reconstructions are bladder augmentations because most of these patients do not require cystectomy. Another fundamental difference compared with adult surgery is the potential for the bizarre and complex anatomy associated with congenital disorders, such as bilateral ectopic ureters and cloacal exstrophy.

The principles of any continent diversion are universal. The ideal storage device is a low-pressure reservoir that does not leak urine or reflux, and has a simple and effective means of emptying. Whenever possible, augmentation of the native, in situ bladder is preferred to avoid the potential complications associated with a ureteral-intestinal anastomosis. CURs are mandatory, however, when the native bladder is absent or not salvageable. Patients with syndromes associated with bladder agenesis, cloacal exstrophy, and pelvic organ destruction secondary to trauma or malignancy would be candidates for a CUR.

Although common in pediatric urology, the decision to pursue a continent diversion must be weighed against the risk of potential morbidity. Although techniques for gastrointestinal urinary reservoirs are plentiful and commonly used, they are associated with significant complications.[47] Meticulous preoperative, intraoperative, and postoperative care and attention to details are necessary to ensure satisfactory outcomes.

Patient Evaluation and Selection

The patient, the family, and the entire health care team must be involved in the decision to pursue a continent urinary diversion. The common complications, including UTIs, difficulty catheterizing, metabolic abnormalities, and stone formation, and the more serious and life-threatening complications, including bladder perforation and risk of malignancy, must be discussed and understood.[48-53] Everyone involved in caring for the child must be committed to the appropriate postoperative care, including regular CIC and bladder irrigation.[48,50,54]

Clinical evaluation requires a thorough history and physical examination. Particular attention should be paid to latex allergies or precautions because this can be a fatal complication. Preoperative evaluation should include upper urinary tract imaging with a renal-bladder ultrasound and renal scan and a voiding cystourethrogram. Serum chemistries are required because impaired renal function may alter which gastrointestinal segment is considered.[50] Initially, it was suggested that a creatinine clearance of less than 60 mL/min might be a contraindication for the use of ileum as a continent urinary reservoir,[55,56] but augmentation often stabilizes renal function, and reconstruction can be safely performed before renal transplantation.[57] Urodynamic studies are necessary to determine outlet resistance, bladder capacity, and storage pressures.

The net result of these investigations is a comprehensive surgical plan. The exact procedure depends on which gastrointestinal segments are to be used, and whether the patient requires concomitant ureteric reimplantation, bladder neck procedure, or a continent catheterizable channel. Patients with a neuropathic bladder frequently undergo a simultaneous Malone antegrade continence enema (MACE) procedure using the appendix to achieve fecal continence.[58] The need for this procedure must also be factored into the type of reconstruction needed because it likely mandates a urinary catheterizable channel constructed from ileum. Our institution has found that a single comprehensive reconstructive surgery (total continence reconstruction) has equivalent outcomes compared with a "staged" approach, with separate operations for these procedures.[59] Total continence reconstruction is very beneficial because family members interested in urinary continence usually appreciate a MACE procedure for fecal continence, and simultaneous surgery avoids a second laparotomy.[59]

Preoperative preparation usually involves bowel preparation, but there is no consensus on a standardized approach. Despite the current trend away from a formal bowel preparation in adult exenterative surgery, we believe that patients with spina bifida warrant special consideration. The degree of constipation and stool impaction cannot be underestimated, and mandates an aggressive approach. We also believe that the presence of a ventriculoperitoneal shunt mandates appropriate perioperative antibiotics and a sterile urine culture because an infected ventriculoperitoneal shunt is a major morbidity that should be prevented with aggressive prophylactic measures.[60]

Long-term follow-up is required with all patients. After the postoperative visit, and assuming the absence of complications, the patient should be seen at least semiannually with a history, physical examination, creatinine and electrolytes, and an ultrasound scan performed. Because of the concern of malignant transformation, cystoscopy should be performed annually beginning 10 years from the initial bladder augmentation.[48,50]

Continent Urinary Reservoirs

Although rarely encountered, several specific childhood diagnoses, such as bilateral ectopic ureters, bladder agenesis, or bladder malignancy, require complete bladder replacement, and a CUR allows urinary continence. Patient selection for the procedure is extremely important because noncompliance with catheterization would result in myriad complications, despite a technically perfect operation. If there is doubt as to the reliability of, or support for, the patient, he or she would be much better served with an incontinent diversion, such as an ileal conduit.

Although the gastrointestinal tract again provides for the most common and popular reservoir, several key differences exist compared with a bladder augmentation. Colon and stomach are more commonly used because the musculature of the taeniae coli and stomach allow for a more reliable ureteric and catheterizable channel implantation. Numerous operations have been described, but these can generally be placed into three categories: a reservoir fashioned solely from ileum (i.e., Kock pouch), a gastroileal composite reservoir, and an ileocecal reservoir (Indiana pouch).[61] These techniques have multiple variations described, and because the published reports in children are usually limited to small numbers with a lack of direct comparison, it is impossible to identify the ideal reservoir for children.[54,61,62] The reconstructive surgeon must be familiar with several techniques because each has advantages and disadvantages that must be tailored to each unique clinical scenario.

Kock Pouch

Kock first described a continent ileostomy in 1971,[63,64] and from this the Kock pouch was developed in 1982.[65] This continent ileal reservoir was among the original nonorthotopic bladder substitutions used, and it remains popular today.[47,66,67] Continence and prevention of reflux are attained via afferent and efferent limbs fashioned with nipple valves. This technically demanding aspect usually requires the use of stapling devices, and these can be the source of the most significant complications (e.g., stone formation) and long-term failure rate.[68]

Approximately 80 cm of distal ileum is harvested in adults, with the proximal 15 to 20 cm used in an isoperistaltic fashion to create the antireflux mechanism, and the distal 12 to 15 cm used for the continent cutaneous stoma. These lengths are decreased appropriately depending on the size of the patient. The bowel is intussuscepted through its full thickness and is secured by three rows of staples, although the use of absorbable mesh has also been described.[69] Several technical modifications to overcome the more common complications have been described, including removing the distal six staples from the device,[70] stripping the distal mesentery,[71] and the use of absorbable staples.[72]

Gastroileal Pouch

A composite reservoir consisting of gastric and ileal segments maximizes the advantages of both, while offsetting their complications. The metabolic derangements potentially

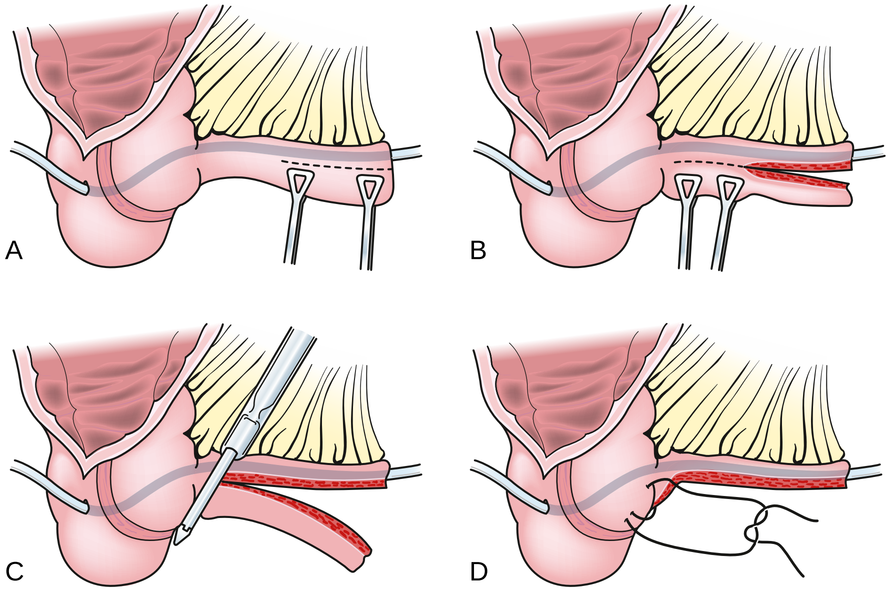

Figure 56-4 **A-D,** The Indiana pouch uses the tapered and reinforced ileocecal valve as the continence mechanism and the cecum for urinary storage. (From Cain MP, Metcalfe PD, Rink RC. Urinary diversion. In: Docimo SG, Canning DA, Khoury AE, eds. *Clinical Pediatric Urology*. 5th ed. Boca Raton, FL: Informa Healthcare; 2007, Figure 57.22.)

complement each other because the acidic gastric secretion neutralizes the metabolic acidosis of colon or ileum.[73-75] Gastric segments, in isolation, have been shown to have lower risks of UTIs and bladder calculi.[76-78] In patients at high risk for short gut syndrome, as in cloacal exstrophy, it allows a minimum of valuable absorptive tissue to be lost.[48] It is a significantly more complex reconstruction, however, with a risk of hematuria-dysuria syndrome, but is a valuable alternative for selected patients.[79]

Indiana Pouch

The use of the ileocecal segment was developed and popularized to take advantage of the ileocecal valve as a continence mechanism. Many surgical techniques have been described to improve cutaneous continence, to simplify the surgical procedure, and to minimize complications. The Indiana group modified the pouch described by Gilchrist and associates[80] with a unique plication method that has remained popular. An Indiana pouch uses the detubularized cecum as its reservoir, with ureters implanted in a nonrefluxing manner into the taeniae. The distal ileum is narrowed and plicated into the ileocecal valve, which is reinforced by Lembert sutures, and brought to the skin as a continent catheterizable channel (Fig. 56-4). Continence has been reported in 95% to 99%,[80a, 81] in part owing to the large capacity and compliance of the reservoir.[82] Complication rates have been acceptable (0.6%),[80a] but not all surgeons have reported such success.[83] Although the Indiana pouch has achieved great popularity in adult patients, its use has been limited in children because the removal of the ileocecal valve can lead to late development of diarrhea and vitamin B_{12} malabsorption.

MAINZ Pouch

The MAINZ (*m*ixed *a*ugmentation of *i*leum '*n* *z*ecum) pouch was introduced by Thuroff and colleagues in 1985[84] as an ileocecal reservoir with two limbs of distal ileum. It has undergone multiple variations and has been well accepted worldwide, in part because of its numerous applications as a rectosigmoid pouch,[84] continent urinary reservoir, bladder augmentation,[84] and an orthotopic bladder substitute.[85] The same group have also published several reports on their experience in children.[86-88]

The rectosigmoid pouch (MAINZ pouch II) was used predominantly in patients with bladder exstrophy, after either failed primary reconstruction or as a means of undiversion from an incontinent diversion. All 38 children reported daytime continence; 8.6% required some protection overnight. Sixteen percent required revision of their ureteric anastomosis because of either stenosis (7 of 69 renal units) or reflux (3 of 69 renal units). Renal function was normal in all patients, and 69% required medical therapy for acidosis. Annual rectosigmoidoscopy was begun 10 years after surgery, and all 16 patients have been free of tumor, with a maximal follow-up of 15 years.[89]

The same group reported on their extensive use of the MAINZ pouch as a continent urinary reservoir in 2005.[86] The primary indication was for neuropathic bladder in 70 children, with 53 myelomeningocele patients and 10 with related neurogenic disorders. The catheterizable channel was created with appendix in 32 patients and an intussuscepted ileal nipple in 26. The remainder consisted of a bowel flap (three patients), tapered ileum (three patients) or a Monti procedure (one patient). Stomas were concealed in the umbilicus, and continence rates are excellent (97%). Six (8.6%) patients required a revision for incontinence, and 29 (41%) underwent revision for stenosis at the skin level. At a mean follow-up of 8.7 years in 65 patients, surgical complications occurred in 57%. This includes 12.7% of renal units that required reimplantation and 10 patients who developed pouch calculi (14%). No patients had evidence of tumor formation.

Thirty-seven patients in this series underwent reconstruction of the ileocecal valve, and 76% reported no increase in frequency of bowel movements compared with 64% of patients without ileal intussusception. No patients with normal preoperative renal function had deterioration in glomerular filtration rate, and none developed metabolic acidosis. The serum base excess increased in 10 patients (15%), however, and 30 (46%) were using prophylactic alkali substitution.[86]

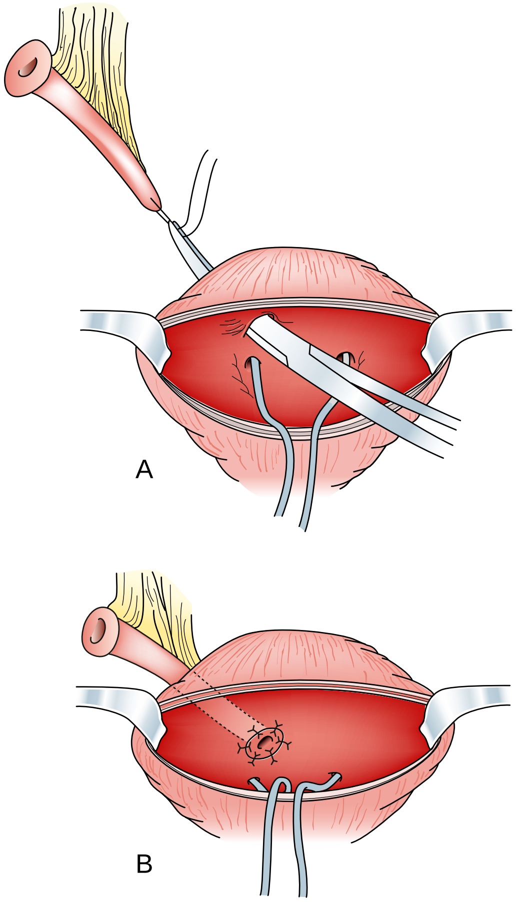

Figure 56-5 Mitrofanoff principle. **A,** The appendix is readily accessible and mobilized with its vasculature. **B,** It is implanted easily beneath the bladder mucosa to provide a reliable catheterizable channel.

Continent Catheterizable Channels

CURs and augmented bladders have severely limited means of spontaneously emptying, with increased consequences of incomplete emptying. Not adhering to a strict CIC schedule can result in an increased risk of UTI, bladder stones,[90] and spontaneous bladder perforation.[91,92] In 1980, Mitrofanoff[93] introduced the principle of a continent cutaneous channel by using the vermiform appendix and implanting it submucosally into the bladder. What is now known as the "Mitrofanoff principle" states that any supple tube implanted submucosally with sufficient muscle backing acts as a flap valve and results in a reliable, continent cutaneous, catheterizable channel.

The Mitrofanoff principle (Fig. 56-5) has been widely embraced and applied to various tissues because the appendix is not always appropriate or available, especially with the popularity of the MACE procedure. The use of stomach, colon, bladder, ureters, and fallopian tubes has been reported with good success.[94-106] The reconfigured ileal channel was introduced by Yang[100] and Monti and colleagues,[95] and has assumed a leading role in genitourinary reconstruction because of its reliability with a minimal loss of bowel. Casale introduced the spiral Monti, which increases the potential length to 14 cm and a diameter of 12F to 14F.[105]

A continent catheterizable channel requires a supple tube, straight path, and short intra-abdominal segment. An appendicovesicostomy requires full mobilization of the right colon and mesoappendix to ensure adequate mobility and blood supply. If increased length is desired, a cecal cuff may be used.[94,107] The Monti-Yang technique (Fig. 56-6) requires isolating 2 cm of ileum, opening it along its antimesenteric border, and retubularizing it in two layers over a 12F or 14F catheter. Instead of a simple retubularization, the spiral Monti channel uses a 3- to 4-cm length that is opened in the midline, detubularized on opposing sides of the mesentery, and retubularized to form a longer channel (Fig. 56-7).[105] The channel is implanted submucosally into detrusor because the thick muscular wall is ideal for a continent valve; however, stomach and taeniae coli have been used successfully. Reimplantation into ileum is the most challenging and requires the creation of a seromuscular trough, or a Ghoniem-type reimplantation. We have found it useful to secure the ileal augment/bladder to the posterior fascia along the entire length of the implanted channel to prevent chronic thinning of the muscular backing and eventual incontinence.

Several authors have described continent catheterizable tubes fashioned from native bladder. Casale's original description of the "intravesical channel"[108] was modified by Rink and colleagues.[109] Although continence rates of 100% were reported, the technique is hampered by a 45% incidence of stomal stenosis. Although still a useful technique if an intraperitoneal procedure can be avoided, it has been largely replaced by appendicovesicostomy and reconfigured ileovesicostomy.

We prefer implantation of the channel along the posterior wall of the bladder because this allows for the straightest and most direct path from the abdominal wall to the bladder (Fig. 56-8). Alternatively, placement of the channel along the anterior bladder wall allows for the detrusor to be tacked to the anterior abdominal wall, which provides more posterior backing for the channel. A posterolateral course may benefit the sensate patient because it is less likely to irritate the trigone with each catheterization.

The stoma site can be hidden within the umbilicus or placed in the right lower quadrant, depending on surgeon preference and patient habitus. The umbilicus has the advantage of being accessible above the pant line, but requires a longer intra-abdominal course. A stoma in the right lower quadrant ensures that the detrusor is securely fixed to the abdominal wall, with a shorter intraperitoneal course and less unsupported channel, and is hypothetically less likely to result in channel laxity and difficulty of catheterization. The detrusor can be elevated up to the wall, even in the smallest bladders, by slightly offsetting the initial incision when bivalving the bladder, and bringing a Boari flap to the posterior abdominal wall.

Regardless of location, great care is taken to ensure that a catheter, usually 12F to 14F, passes easily, and that the channel is as straight and tension-free as possible. When satisfied, the surgeon fixes the channel and reservoir to the abdominal wall with a permanent suture. Many ingenious skin flap techniques have been employed to minimize the chance of stomal stenosis, all inserting into the spatulated channel. An indwelling catheter is left for 3 weeks, and the first catheterization is usually performed in the clinic setting. The suprapubic tube is left in situ until everyone is certain that there are no difficulties with catheterization. All family members caring for the child must learn proper catheterization technique.

Stomal continence is excellent, and rates of 90% to 99% are reported in the largest published series.[61,97,110] Complications pertain primarily to difficulties with catheterization, and these can be categorized into difficulties that occur at the skin level and difficulties that occur deeper, at the entrance to the bladder. This is an important differentiation because a skin

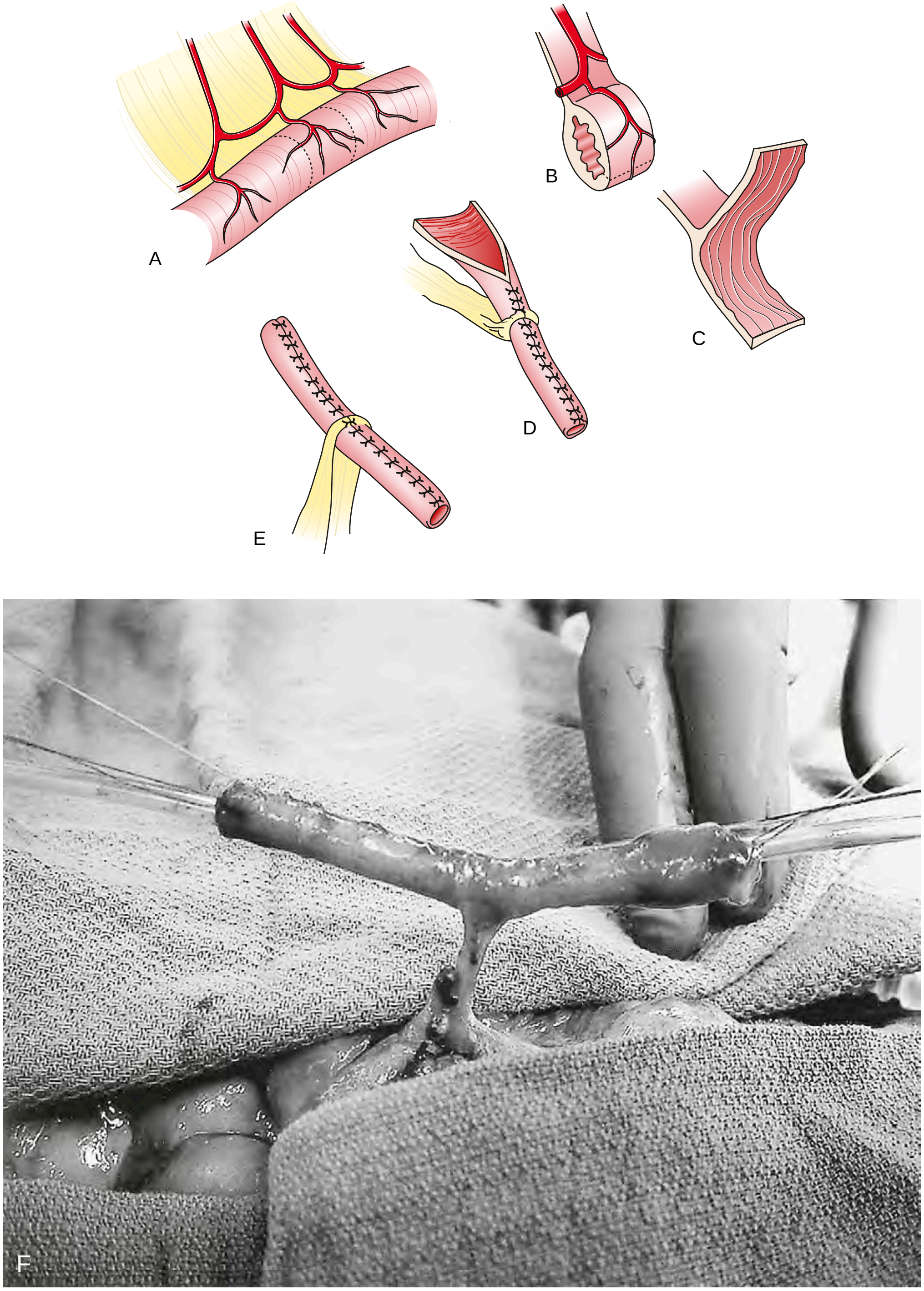

Figure 56-6 **A-E,** The Monti-Yang channel is constructed from a 2-cm segment of ileum that is opened on the antimesenteric border and retubularized longitudinally. **F,** The reconstructed Monti-Yang channel has the advantage of a centralized mesentery.

revision is a simple outpatient procedure, whereas a deep revision requires a much more extensive dissection, usually a laparotomy. Stomal stenosis is reported to occur in 5% to 25%,[61,111] with nearly identical rates between appendiceal and tapered ileum channels.[97,112]

These channels provide a more convenient and more socially acceptable means of catheterization, and have been shown to increase patient compliance with their CIC regimen.[113] It is especially beneficial for patients with a sensate urethra, and in obese or wheelchair-bound women. The Mitrofanoff channel also facilitates ease of caregiver catheterization, comfort, and, most importantly, patient independence.

COMPLICATIONS FROM THE INCORPORATION OF INTESTINE IN THE URINARY TRACT

Despite the popularity of using the gastrointestinal tract as a urinary reservoir, the potential complications are numerous and can be significant. A broad categorization of these

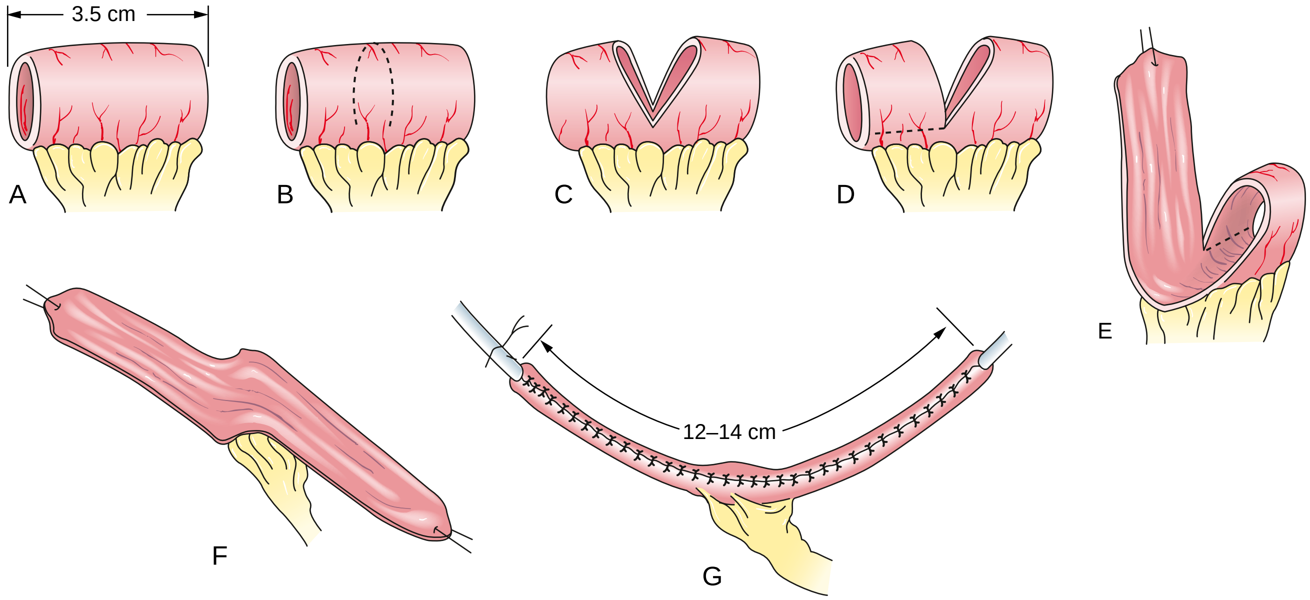

Figure 56-7 **A-G,** The Casale spiral Monti channel is created by incompletely dividing the bowel segment in the middle, opening on opposite sides of the mesenteric border, then retubularizing to provide a much longer tube than the standard Monti-Yang technique.

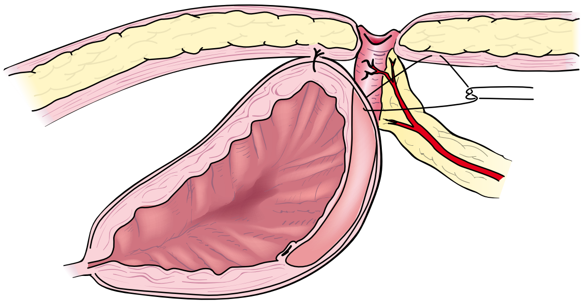

Figure 56-8 The Mitrofanoff channel is secured to the posterior bladder wall with a direct, straight, short path from the abdominal wall to the bladder. (Courtesy of Indiana University Medical Illustration Department.)

complications includes (1) complications owing to structural defects, (2) complications secondary to the loss of the intestinal segment, (3) complications owing to secretions, and (4) complications resulting from absorption (Table 56-1). Because the complications are similar, and the experience with bladder augmentation is much more prevalent, much of our data on complications are from bladder augmentation series.

Table 56-1 **Complications Resulting from Using the Gastrointestinal Tract as a Urinary Reservoir**

- Structural complications
  - Reaugmentation
  - Perforation
  - Bowel obstruction
  - Malignancy
- Loss of intestinal segment
  - Bowel dysfunction
  - Vitamin deficiency
- Secretions
  - Acid
    - Hematuria dysuria syndrome
    - Metabolic alkalosis
  - Mucus
    - Bladder calculi
    - Urinary tract infection

Structural Complications

Structural complications include the requirement for a reaugmentation, spontaneous perforation, and long-term malignancy potential. A secondary augmentation was required in 9.4% of augmentations in our series of 500 augmentations.[76] The most common indication for reaugmentation was for persistent high intravesical pressures from bowel contractility.[114,115] The hallmark clinical signs are incontinence or hydronephrosis with screening ultrasound, and this is confirmed by urodynamic studies. This complication occurred a mean of 7 years after the original augmentation, and was least likely when ileum was used.[76] Whenever a laparotomy is required—to perform a urinary diversion incorporating a gastrointestinal segment—this places the patient at risk for a bowel obstruction, which occurs in approximately 3% of cases (3.2% in the Indiana bladder augmentation series).[76,116-118]

The spontaneous perforation of an augmented bladder or CUR can be a fatal complication, and must always be a consideration in any patient with a prior CUR who presents with abdominal pain. In the immediate postoperative period, urinary ascites is likely due to technical error with the anastomosis, but a late perforation usually originates in the bowel, approximately 1 cm from the posterior anastomotic line.[48] Any delay in presentation, which is common in the neuropathic population with the high prevalence of sensory abnormalities, increases the risk of sepsis and death.

A high index of suspicion with early and aggressive diagnostic studies is essential. Diagnosis is most reliable with a computed tomography cystogram, and treatment is usually by laparotomy and primary closure.[91] Conservative treatment with catheter drainage has been successful in selected patients.[119] We have had 43 augmentation patients (8.6%) with a perforation, with 9 patients having two perforations, and 1 with three separate perforations. A higher risk was calculated whenever sigmoid segments were used and bladder neck surgery was performed. A lower risk was incurred, however, if a catheterizable channel was present.[51] Although it is commonly believed that a CUR may be less likely to perforate, the risk may be higher than previously reported.[120] Perforation in a Koch reservoir was reported in 2 of 20 Swedish children, at 6 and 9 years postoperatively.[47]

The development of an adenocarcinoma is a concern whenever the urinary and gastrointestinal tracts are combined. This development was first recognized with ureterosigmoidostomy, and has since been reported in all manner of diversions.[42,121-124] In the ureterosigmoidostomy, the tumor usually arises from the ureterointestinal junction, and its incidence has been estimated to be 7000-fold higher than the general population.[42] Although a tumor has been reported 3 years after augmentation,[125,126] the mean predicted latency is 21.5 to 26 years.[38,42] Although most surgeons appreciate the risk, definitive guidelines for surveillance have not been established. Annual cystoscopy has been recommended to begin 3 to 10 years after augmentation.[38,48]

Austen and Kalble[38] reviewed the world literature and identified 81 tumors collectively in various continent and incontinent diversions with incorporated bowel segments. This total is exclusive of the large number of malignancies reported after ureterosigmoidostomy. Neoplasia was reported in 12 ileal conduits and 5 colon conduits with a mean latency of 22 years and 10 years. Colon conduit tumors were exclusively adenocarcinoma, and ileal conduits showed transitional cell carcinoma, squamous cell carcinoma, carcinoid, and anaplastic tumors.

Loss of Intestinal Segment

The removal of a gastrointestinal segment for CUR or augmentation is usually well tolerated; however, bowel dysfunction has been reported in 10% to 54% of patients.[127,128] Removal of the ileocecal valve can result in problematic diarrhea and rectal incontinence, especially in neuropathic patients.[129,130] Because bile salts are absorbed in the distal ileum, their increased quantity results in a significant osmotic gradient and problematic diarrhea.[131] Leaving the distal 15 to 20 cm of distal ileum intact can usually prevent this complication. Treatment of mild cases is usually successful with anion-exchange resins.[50]

Vitamin B_{12} deficiency can develop in 35% of patients after an 80-cm small bowel resection for a Kock pouch,[132] but it has not been shown after ileocystoplasty,[133,134] perhaps because it is limited to a 25-cm resection in children. The Swedish series on Koch reservoirs showed 2 of 20 patients with serum levels of vitamin B_{12} below normal, with 5 patients having low serum folate levels.[135] Most metabolic problems were seen in patients who were younger than 16 years at reconstruction.[135]

Complications Owing to Secretions

Gastrointestinal mucosa continues to secret mucus, and this predisposes the patient to UTIs and bladder stone formation.[48] Bladder stones occur in approximately 10% to 30% of augmentations and CURs.[77,136,137] The high incidence of struvite composition implies a common etiology with a urease-producing bacteria, although this may also be due to high levels of calcium and phosphate in mucus.[138] The systemic acidosis common to patients with augmentations decreases stone inhibitors and promotes stone growth.[90] Prevention is aimed at regular CIC and daily bladder irrigations. Treatment is amenable to open or endoscopic means,[90,136,139,140] with open surgery reserved for the larger stones.

The acidic nature of gastric secretions can result in a hematuria-dysuria syndrome in 9% to 70% of bladder augmentation patients.[48,141-143] This is much less of a problem, however, in a composite gastroileal CUR because stomal incontinence is much less likely, and the ileal segment helps neutralize the secretions.[75]

Bacteriuria is nearly universal in any patient performing CIC, especially when combined with mucus from a bowel segment. A UTI most frequently manifests with malodorous urine, but symptoms also include hematuria, de novo incontinence, suprapubic pain, or increased mucus production.[48] Rink and colleagues[118] reported a symptomatic UTI in 22.7% of patients with an ileal augmentation, and in only 8% of patients with a gastrocystoplasty. Treatment of asymptomatic bacteriuria is not indicated unless culture indicates a urease-producing or a very virulent organism. Treatment may decrease the risk of stone formation, however.

Complications Resulting from Absorption

The use of bowel as a urinary reservoir can be associated with profound metabolic changes owing to its absorptive nature. Colon and ileum readily absorb ammonium, hydrogen ion, and chloride, and this can result in a hyperchloremic metabolic acidosis. This metabolic acidosis is tolerated in many patients with normal renal function,[144] but may require medical therapy in others. The extent of ion absorption depends primarily on intestinal contact area and length of time for contact; significant acidosis should prompt an investigation into incomplete emptying.[48] Although not all patients are frankly acidotic, many have an increase in their serum chloride levels, albeit still in the normal range.[66,116] The acidosis prompts mobilization of buffers, and can result in bone demineralization. Although some authors believe that somatic growth impairment occurs, it remains controversial. This growth impairment has been shown in animal models,[145-147] and in patients with bladder exstrophy, where there has been a reported 15% to 20% decease in overall height.[148] In the much more prevalent myelodysplasia population, the clinical correlation has been more difficult to prove. The acidosis also results in hypocitraturia, and increases the risk of renal and bladder stone formation.[90]

Finally, medications such as phenytoin and methotrexate are readily absorbed across the bowel, and levels must be closely monitored.[149] Glucose is also absorbed, making urinary monitoring of hyperglycemia unreliable.[150]

CONCLUSION

A low-pressure conduit or reservoir is fundamental to preserving renal function, and this is the primary goal of urinary diversion. With CIC and pioneering surgeons, lower urinary tract reconstruction has evolved significantly, and even the most complex patient can expect to achieve urinary continence. Although there have been enormous gains in independence and social well-being in affected children, this type of reconstruction has provided an entire new set of complications, some of which are potentially lethal. It is of fundamental importance that these long-term risks are understood by the surgeon and the family. All of these children require a dedicated team approach; the family, surgeon, and nursing personnel must work together from preoperative planning through the lifelong follow-up that is required.

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CHAPTER 57

AUGMENTATION CYSTOPLASTY

Mark C. Adams and Richard C. Rink

Since the acceptance of clean intermittent catheterization (CIC) as a reliable means of emptying the urinary bladder,[1,2] augmentation cystoplasty has provided an effective surgical means of enlarging the bladder, while maintaining low pressure. A compliant urinary reservoir is essential in achieving urinary continence safely, and can often be accomplished using medical therapy no matter the patient diagnosis. Bladder augmentation is reserved for patients who do not respond to or tolerate therapy using anticholinergic medications with or without CIC. It is most often done to achieve continence, but may occasionally be required because of infection or hydronephrosis caused by high intravesical pressure. Prompt recognition and more effective early medical management of bladder dysfunction in patients with spina bifida, urethral valves, exstrophy, and other urologic problems may decrease the future need for augmentation cystoplasty,[3] but it is unlikely to be able to avoid it altogether.

The pathophysiology of bladder dysfunction can be understood only by performing careful urodynamic evaluation; such studies are routinely done on any patient considered for augmentation cystoplasty, and often are required in a serial fashion to evaluate the response to medical management. The studies should not be done during or immediately after acute cystitis because inflammation may temporarily impair bladder compliance. Joseph[4,5] showed that rapid infusion of cold irrigant during cystometrography may likewise result in a false-positive finding of an inadequate reservoir. Special care must be used in evaluating the bladder defunctionalized by a diverting vesicostomy or one served by an outlet with little to no outlet resistance. Placement of a balloon catheter in the vesicostomy or at the bladder neck may allow bladder filling during the study, but may inadequately predict future bladder capacity or compliance with “functionalization.”[6]

Safe urinary continence requires a reservoir that can hold 3 to 4 hours of urinary volume at pressures less than 20 cm H_2O; sustained pressures greater than 40 cm H_2O are deleterious.[7] This volume may vary among patients and be quite high in some with renal damage. Augmentation cystoplasty is considered when such a bladder cannot be provided by conservative or medical therapy. Urinary continence also depends on adequate outlet resistance and bladder emptying. Both should be assessed during good urodynamic evaluation because they potentially require treatment and are not improved by bladder augmentation alone. Augmentation often worsens bladder emptying by interfering with sustained bladder contraction. Each patient and family must be reliably capable of and committed to performing CIC before consideration of augmentation cystoplasty because the patient is likely to require it afterward regardless of the underlying diagnosis.

PATIENT EVALUATION AND PREPARATION

Besides thorough urodynamic evaluation, each patient considered for augmentation cystoplasty should undergo upper urinary tract imaging and generally will have done so on a regular basis. Ultrasonography is typically used, although nuclear renography with a catheter in the bladder may be indicated for hydronephrosis. Vesicoureteral reflux can be excluded during videourodynamic evaluation or by voiding cystography. Renal insufficiency and acidosis are important to recognize preoperatively because acidosis in particular may worsen after intestinal cystoplasty. Such problems are usually suggested by findings on upper tract imaging and may be confirmed by serology. A 24-hour urine collection may be indicated in some patients to determine the extent of any renal damage, and to document the urine volume produced. For most patients, augmentation cystoplasty has minimal effect on native bowel function; however, a history of underlying chronic gastrointestinal illness should generate concern. General health and nutritional status should be good for patients undergoing cystoplasty. The most important consideration is the commitment of the patient and family to achieving a good result. The patient and family must be ready and able to perform CIC on a regular basis; failure to do so when indicated can result in complications and morbidity despite a technically perfect operation.

The preference of most surgeons is to perform mechanical bowel preparation with polyethylene glycol–electrolyte solution (GoLYTELY) on each patient scheduled to undergo cystoplasty. Even if gastrointestinal cystoplasty or ureterocystoplasty is planned, intraoperative findings may dictate use of an intestinal segment. Profound constipation in patients with neuropathic bowel may make good mechanical bowel preparation difficult. The child can be started on a clear liquid diet and can be given oral magnesium citrate or polyethylene glycol–electrolyte solution (GlycoLax) and enemas at home 2 days before hospitalization. Although the need for mechanical bowel preparation has been questioned, we prefer that a patient with neuropathic bladder receive mechanical preparation in the hospital on the day before surgery so that progress of the cleansing can be monitored, and the patient can be kept well hydrated. Great care should be taken with mechanical bowel preparation in children with renal insufficiency. Parenteral antibiotics are given preoperatively, and sterile urine should be documented. This is particularly true if the child has a ventriculoperitoneal shunt.

GASTROINTESTINAL CYSTOPLASTY

Operative Technique

Regardless of the gastrointestinal segment used for augmentation cystoplasty, the initial incision is generally made in the lower midline from pubis to umbilicus. This incision allows access to the entire abdomen, and additional exposure can be obtained easily by extending the incision superiorly. In particular, it provides superb exposure for creation of a continent stoma at the umbilicus. A lower Pfannenstiel incision can be used, but may limit exposure. Initial laparoscopic mobilization of bowel may insure that a lower transverse incision is adequate.[8] Laparoscopic bladder augmentation has

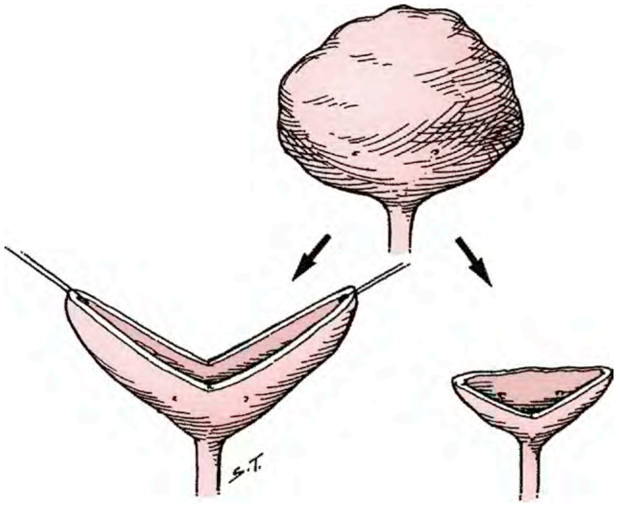

Figure 57-1 Two ways to prepare the bladder for gastrointestinal cystoplasty. Wide sagittal incision to bivalve the bladder (*left*) and supratrigonal cystectomy (*right*). (From Rink RC, Adams MC. Augmentation cystoplasty. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: Saunders; 1996:917.)

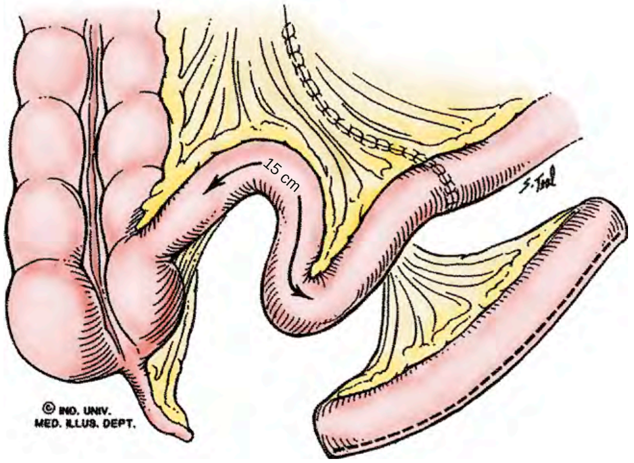

Figure 57-2 The ileal segment is isolated 15 cm proximal to the ileocecal valve, and a two-layer ileoileostomy is performed. The isolated segment is detubularized on the antimesenteric border. (From Rink RC. Bladder augmentation: options, outcome, future. *Urol Clin North Am.* 1999;26:111-123. © Indiana University Medical Illustration Department.)

been reported.[9] If a gastric segment is to be used, a midline incision is required and must extend from pubis to xiphoid. After the lower abdomen is opened and the prevesical space exposed, bladder procedures such as ureteral reimplantation or bladder neck reconstruction are performed before opening the peritoneum to minimize third-space fluid loss. If a ventriculoperitoneal shunt is present, it should be wrapped in an antibiotic-soaked sponge and packed away from the field of dissection after the peritoneum is incised.

The bladder is usually incised in the sagittal plane from within centimeters of the bladder neck anteriorly to the interureteric ridge posteriorly (Fig. 57-1) to allow creation of a wide anastomosis of the gastrointestinal segment and bladder. The incision may be offset to allow a larger right portion of the bladder for easier implantation of a catheterizable channel. A second transverse incision near the dome can create a stellate opening for wider anastomosis if necessary. With a small bladder, it may be useful to make a broad U-shaped incision on the anterior bladder with the open end at the dome. When the anterior flap is rotated superiorly, this incision leaves the bladder as a long, broad strip that can reach toward the umbilicus and provides a nice platform for placement of a continent wall stoma. The native or "diseased" bladder does not need to be resected in the typical pediatric patient.

Careful inspection of the bowel mesentery is important before isolation of the intestinal segment to be used to ensure an adequate blood supply and mobility to reach the bladder without tension. If a segment of intestine is also to be used to create a continent catheterizable stoma, it should be harvested at one end of the isolated segment for cystoplasty. Particular care must be taken to visualize an appropriate vascular mesentery to support both segments, although they typically do not have to be separated very far apart. When the ideal segment is identified, mesenteric windows are made at either end, and the bowel is incised. The bowel is cleared of mesentery at the ends so that a hand-sewn or stapled bowel anastomosis can be performed without inclusion of mesentery. The isolated bowel should be irrigated clear with 0.25% neomycin before reconfiguration.

Intact tubular intestine can generate pressures of 60 to 100 cm H_2O[10-13] by either peristalsis or unit contraction. These pressures can be reduced by reconfiguring the isolated segment.[14,15] This reconfiguration is achieved by opening the segment entirely along the antimesenteric border and folding the open bowel once or twice against itself in a U or W shape. The folded segment should be added to the bladder in such a way as to create as close to a spherical shape as possible. These actions blunt organized contractions in the bowel segment, but also optimize the volume obtained for a given length of bowel used.

Mathematical models,[16] assuming that a sphere is achieved, can calculate what length of bowel of a given circumference is necessary to reach a certain volume, but are impractical. It is better to make the bladder too large rather than too small. The limbs of the folded segment are approximated using a running 3-0 absorbable suture. Usually, this approximation can be done in one precise layer inverting the mucosa within the eventual lumen. A running, locked suture from within is effective at inversion. Getting a larger purchase of adventitia than mucosa is also helpful, although each pass must include ample submucosa to provide strength to the closure. The same principles should be applied to anastomosis of bowel to bladder.

Alternatively, the anastomosis can be done with two layers of absorbable suture including an inner full-thickness layer and an outer seromuscular layer inverting the first. On completion, a large suprapubic tube is brought out through the native bladder when possible and secured at the bladder exit site with a purse-string absorbable suture. Mesenteric windows are closed by loosely approximating overlying peritoneum, while carefully avoiding vessels near the margin. A perivesical drain is brought out of the pelvis through a separate stab incision, but should be removed early in patients with a shunt that could be contaminated.

Ileocystoplasty

Many experienced reconstructive surgeons consider ileum to be the most compliant intestinal segment for urinary storage, and it is the most commonly used segment for cystoplasty.[17-19] Generally, a segment of ileum 20 to 30 cm in length is appropriate for use, although the length may be adjusted based on the urinary output of the patient or the amount of native bladder present and the patient's age (Fig. 57-2). The distal 20 cm of ileum has unique physiologic responsibilities and should not

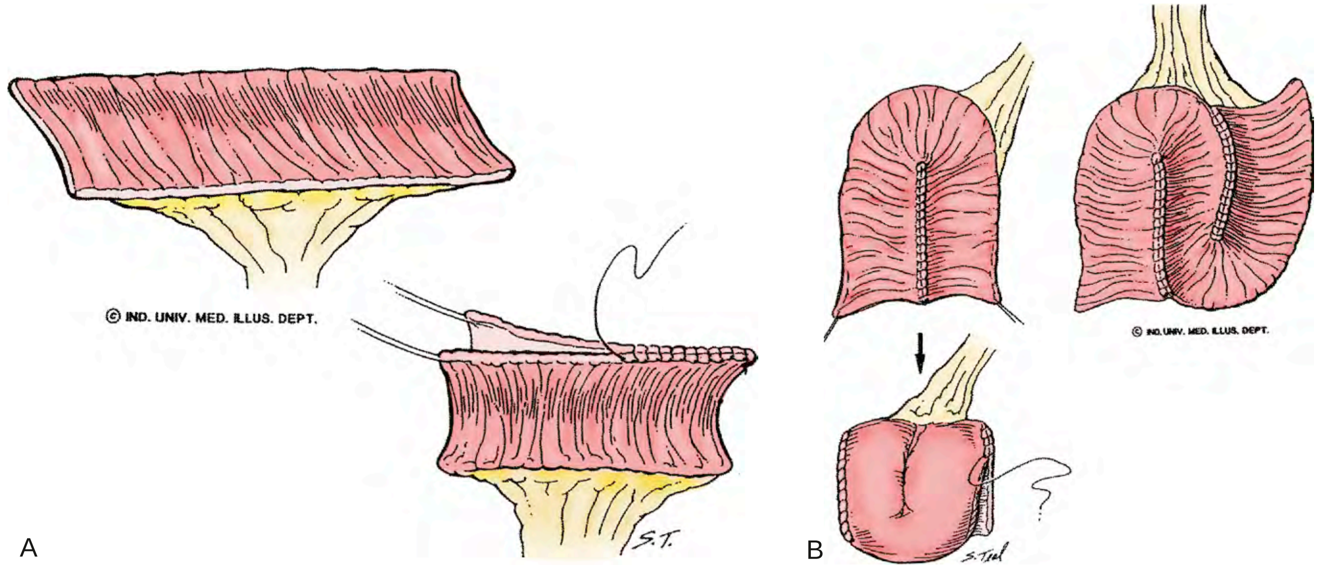
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Figure 57-3 **A,** The detubularized ileum is folded in half, and the medial edges are anastomosed to complete the U patch. **B,** The U patch can be folded further to create a cup of ileum. Longer ileal segments can also be reconfigured as an S-shaped patch. (From Rink RC, Adams MC. Augmentation cystoplasty. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: Saunders; 1996:918-919. © Indiana University Medical Illustration Department.)

be used. The ileum usually has an adequate mesentery, but it should be carefully examined before incision. After incision, the relatively long, narrow segment of isolated ileum can easily be reconfigured in a W or S shape, although a single fold in a U shape is usually effective (Fig. 57-3). The mesentery of the isolated segment should not be twisted or compromised in fitting the segment to the bladder; however, rotation of the segment by 90 degrees is sometimes helpful. Anastomosis of the bowel segment to the posterior bladder can easily be performed first and often from within the bladder. Placement of a catheterizable channel, if necessary, and drainage tube is easily done at that point before completion of the anterior anastomosis, which is usually then done from outside of the bladder.

Ileocecal Cystoplasty

Cecocystoplasty alone is rarely used and so is not discussed. Ileocecal cystoplasty is usually done in its place and is a reliable form of augmentation with the advantage of a constant ileocolic arterial supply. Generally, there are two main types of ileocecal cystoplasties, although many variants have been described. In one, the cecum alone is used as the augmenting segment, and the ileum is used either to reach short ureters or to create a continent stoma by plication.[20] In the other form, the distal ileum one to two times the length of isolated cecum is used as a patch for part of the reservoir as described for the MAINZ (*mi*xed *a*ugmentation with *i*leum '*n* *z*ecum) pouch (Fig. 57-4).[21]

Typically, 15 to 30 cm of ileum and 10 to 15 cm of cecum are used based on volume requirements. When the cecum alone is used as reservoir, its open end can be anastomosed to the bivalved native bladder. The limb of ileum can be plicated to create a catheterizable channel or antireflux mechanism as described for urinary diversion. The appendix can also be used in situ as a catheterizable channel, or an appendectomy is performed if the appendix is not to be used in the reconstruction. Most children undergoing an intestinal cystoplasty may also have neuropathic bowel. Removal of the ileocecal valve from the fecal stream in this group can result in severe diarrhea.[22,23] Cain and Husmann[20] have extensive experience with these segments in children, and they have not observed intractable diarrhea in carefully selected patients. Because of the potential risks of diarrhea and vitamin B_{12} deficiency, use of the segment should be reserved for rare patients with distinct indications.

Sigmoid Cystoplasty

The sigmoid colon has commonly been used for bladder augmentation in pediatric patients with spinal dysraphism because it is often redundant and dilated from chronic constipation. A 15- to 20-cm segment of sigmoid is isolated and removed from the gastrointestinal tract, and a colocolostomy performed (Fig. 57-5A). The segment is isolated from the remainder of the abdominal contents by soaked sponges and irrigated clear with 0.25% neomycin before incision. Early on, Mitchell[24] described incision of the antimesenteric border and closure of the ends of the isolated segment for easy anastomosis to the bladder (Fig. 57-5B). This technique would not adequately dampen contractile activity; it is preferable to fold the open segment in a short U shape as described for ileum (Fig. 57-5C) in a maximum effort to break strong unit contractions of the colon. Regardless of the technique of reconfiguration, the segment can be brought on either side of the native sigmoid reanastomosis and sewn to the bladder.

Gastrointestinal Cystoplasty

Three basic techniques of gastrointestinal cystoplasty have been described. Although superior to augmentation with body in some adult series,[25] antral gastrointestinal cystoplasty with Billroth I gastroduodenostomy has not been used to a significant extent in pediatric patients and is not described here. Gastrointestinal cystoplasty using a wedge-shaped segment of body from the greater curvature gained some popularity in children based on theoretical advantages after an initial report by Adams and colleagues.[26] Although initial enthusiasm has dampened, it may continue to have a place in lower urinary tract reconstruction in selected children.[27] Lastly, a long segment of stomach along the greater curvature, including body

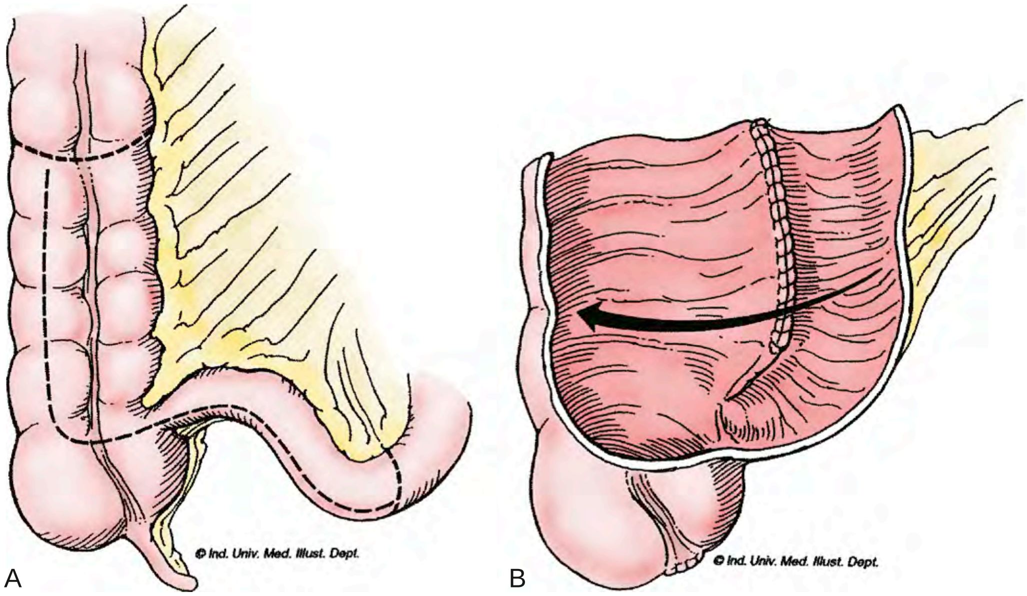
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Figure 57-4 Ileocecal cystoplasty. **A,** Proposed isolation and detubularization of the ileocecal segment. **B,** After detubularization, the medial cecal and ileal edges are approximated. A composite patch is created for anastomosis to the bivalved bladder. (From Rink RC, Adams MC. Augmentation cystoplasty. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: Saunders; 1996:920-921. © Indiana University Medical Illustration Department.)

and antrum, can easily be isolated using a stapler and used in cystoplasty or continent diversion.[28]

In wedge gastrointestinal cystoplasty, the stomach is exposed, and a rhomboid-shaped segment of the body with its base on the greater curvature is outlined (Fig. 57-6A). The segment used may be 10 to 15 cm along the greater curvature and extend near the lesser curvature without going through it to avoid injury to the vagus nerve and its branches. A longer segment provides more surface area for use, approximating that used with ileum or colon. The vessels near the lesser curvature off the left gastric artery just cephalad to the segment to be used are suture ligated in situ before incision to prevent excessive bleeding. Bowel clamps or a stapling device may be placed on either side of the outlined segment to isolate the anterior and posterior wall of stomach. The wedge is next mobilized on a pedicle of the gastroepiploic artery, and the stomach anastomosis is performed in two layers using an inner layer of full-thickness absorbable sutures and an outer seromuscular layer of interrupted silk Lembert sutures (see Fig. 57-6B).

The proximal branches to the stomach from the gastroepiploic vessel are divided to produce a pedicle. Either gastroepiploic vessel may be used, but the vessel on the right is generally more constant. If based on the right gastroepiploic vessel, the segment used generally is further to the left on the greater curvature. Branches from the proximal vessel are divided next to the antrum and pylorus. The segment and pedicle are passed through the transverse colon mesentery and the distal ileal mesentery to reach the bivalved bladder; it is loosely approximated to the retroperitoneum in between. Occasionally, the surgeon must return to the native stomach and ligate more branches from the gastroepiploic artery near its origin to achieve an adequate length of pedicle. Likewise, the initial branches between the pedicle vessel and isolated segment can be divided safely for better length because of the rich submucosal plexus in the gastric patch. The gastric segment fits well onto the bivalved bladder and is anastomosed in a manner similar to that described earlier for ileum or colon.

POSTOPERATIVE CARE

Some morbidity of the operative procedure can be minimized by good postoperative management. Parenteral antibiotics are given until the child is eating and drinking. Fluid and electrolyte status must be closely monitored because third-space fluid losses may be significant in the first several days after surgery. It is imperative that bladder drainage be continuous and free. Mucus production early on is considerable and can easily occlude the drainage catheters. The bladder should be irrigated free of mucus at least three times per day initially and immediately if occlusion of a catheter occurs.

The suprapubic tube is left indwelling for 3 weeks, as are most stents through catheterizable stomas. The suprapubic tube is clamped about 3 weeks postoperatively only after a careful static cystogram showing no leak is performed under low pressure. CIC is begun every 2 hours during the day at that point and every 4 hours at night. The interval between catheterizations can be increased to every 4 hours during the day and every 8 hours at night over the next several weeks. H_2-blockers are given in the early postoperative period after gastrointestinal cystoplasty.[29] Daily bladder irrigation continues indefinitely.

Long-term evaluation includes periodic ultrasound scans of the kidneys and bladder and a plain abdominal film to rule out stone formation. Because of potential metabolic changes, serum creatinine and electrolyte values are also monitored at least yearly. Any deterioration of the upper urinary tract or persistence of incontinence must be evaluated by repeat urodynamics and by a careful history of bladder emptying. It has been suggested that annual or biannual cystoscopy with urine cytology examination be performed beginning 5 years postoperatively for tumor surveillance, but the efficacy has not been evaluated. Daily irrigation to decrease mucus buildup is encouraged and may have a role in decreasing infection and stone formation. Reliable and timely CIC is essential.

Although intra-abdominal adhesions and mechanical bowel obstruction are well-known complications of major abdominal operations, the incidence of bowel obstruction after augmentation cystoplasty is lower than the reported

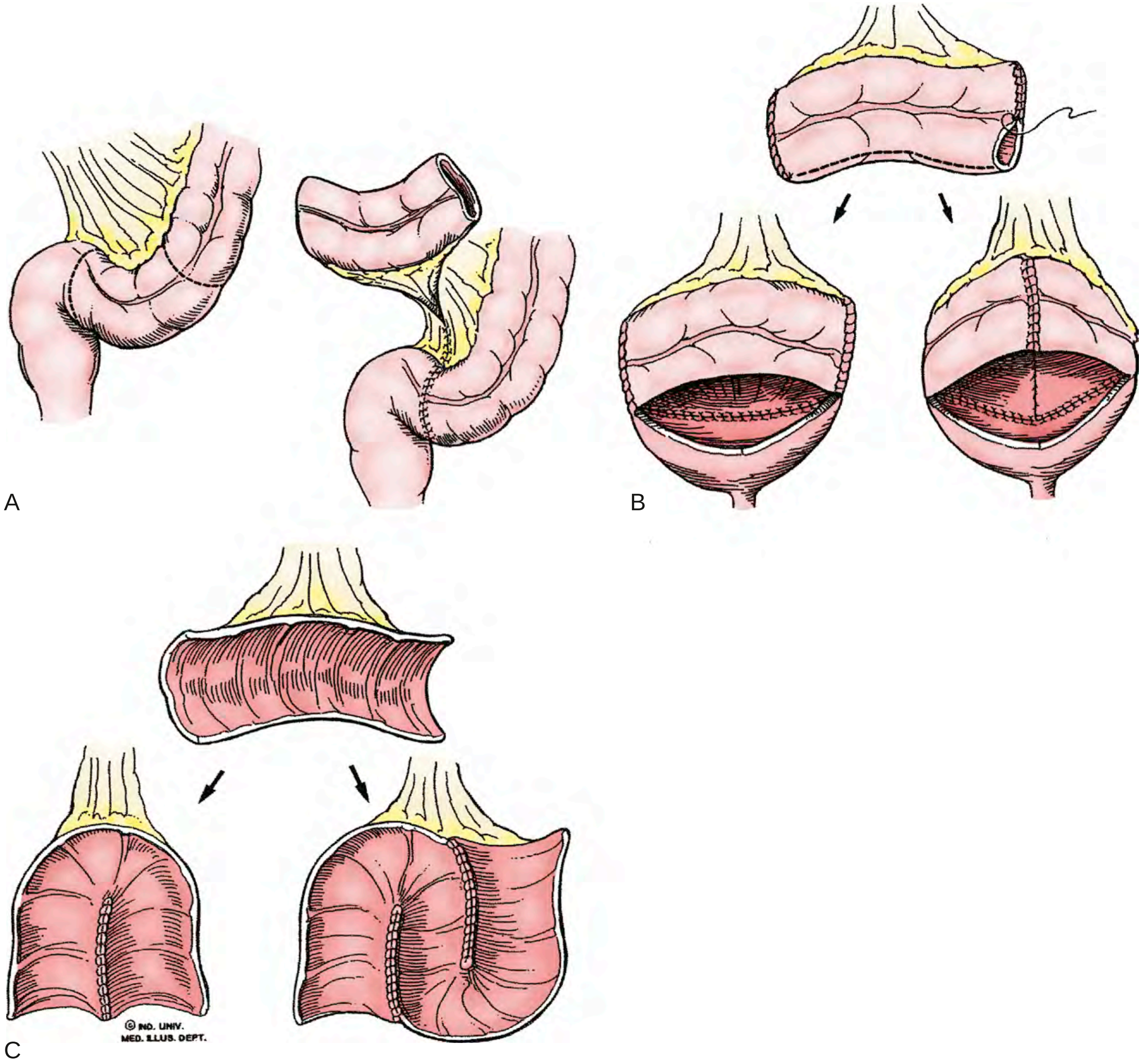

Figure 57-5 Two techniques for sigmoid cystoplasty. **A,** A 15- to 20-cm segment of the sigmoid is divided, and a colocolostomy is performed. **B,** Mitchell technique. The segments can be anastomosed to the bladder in either the transverse or the sagittal plane. **C,** Full detubularization and reconfiguration of the sigmoid reduces high-pressure contractile activity. The authors have abandoned use of the Mitchell technique. (**A** and **B,** From Rink RC, Adams MC. Augmentation cystoplasty. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: Saunders; 1996:919, 920. **C,** © Indiana University Medical Illustration Department.)

rate after creation of a urinary conduit or continent reservoir (5% to 10%, depending on the enteric segment).[30] Mechanical bowel obstruction occurs after augmentation cystoplasty in approximately 3% of cases.[23,31-33] Some studies indicate that it may occur more often after gastrointestinal cystoplasty, including 10% of patients.[32,34] Closure of mesenteric windows, prevention of sites of possible internal herniation, and careful handling of tissue at surgery minimize the risk of obstruction, but do not completely avoid it.

PRIMARY RESULTS

The goals of augmentation cystoplasty are to increase capacity, reduce pressure, and improve compliance. Although some early patients underwent augmentation with a tubular segment of intestine and fared well, the best chance to achieve a good result is by detubularization and reconfiguration of the bowel segment.[14,15] Although Mitchell and Piser[33] suggested that the size and configuration of the bowel segment were more important than the type of bowel segment used, others[19,35,36] have concluded that the ileum is the most compliant gastrointestinal segment for use in cystoplasty. All authors recognize, however, that good results can be achieved in most patients with any gastrointestinal segment if it is used properly.

In a review of patients undergoing augmentation at Indiana University, 19 of 323 patients (6%) required a secondary augmentation owing to persistent pressure.[37] This group later updated their first 500 patients, and noted 47 (9.4%) required reaugmentation. The mean time from the original surgery to reaugmentation was 7.5 years (3 months to 22.8 years).[38] These primary failures included 13.8% of colocystoplasties, 10.4%

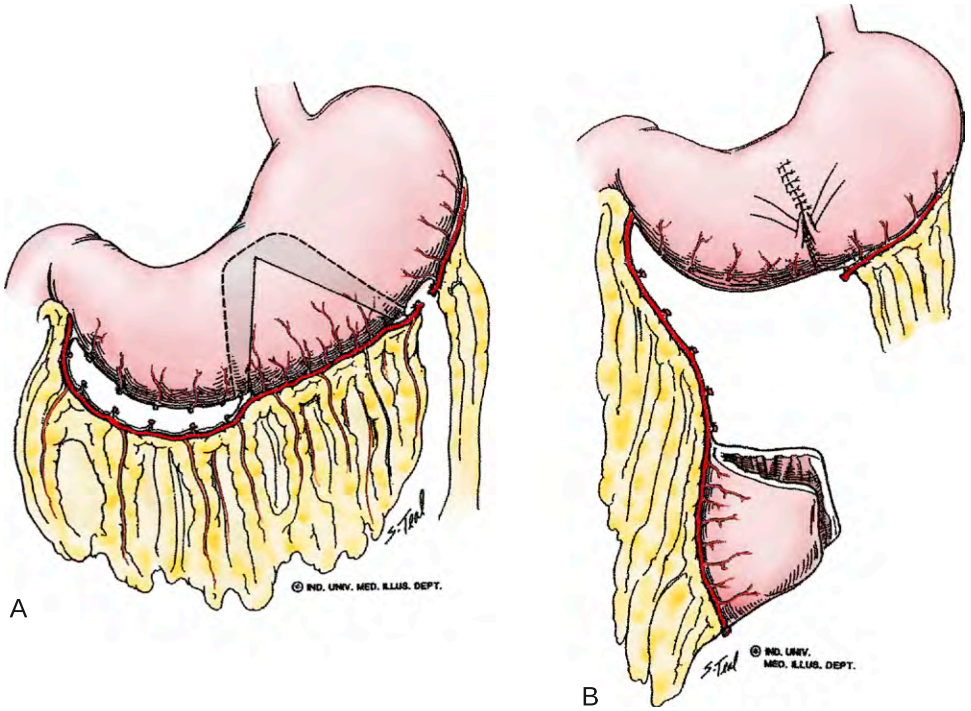
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Figure 57-6 Gastrointestinal cystoplasty. **A,** Isolation of a wedge from the greater curvature. Short gastric vessels are ligated and divided, and the gastroepiploic artery is divided distal to the patch. **B,** The patch is extended on its pedicle, and the stomach is closed in two layers. (© Indiana University Medical Illustration Department.)

of gastrointestinal cystoplasties, but only 1.4% of ileocystoplasties.[37] Evaluating continent urinary reservoirs in adults, Berglund and colleagues[39] and Studer and Zingg[36] noted lower basal pressures and less motor activity in ileal reservoirs compared with cecal reservoirs.

There are series of patients with better results after colocystoplasty than noted in Indiana[40]; in most, the sigmoid segment was folded rather than simply closed on the ends. Likewise, the segment of stomach used in early gastrocystoplasties was small in surface area; using a larger, rhomboid-shaped segment may decrease the risk of issues with compliance, but does place more acid-producing cells in the bladder.[41] No clinical study has ever critically compared the different segments while controlling for surface area and the exact technique used. Most failures with any segment are the result of rhythmic sinusoidal pressure contractions that generate too much pressure too early in filling. Such contractions of low amplitude late in filling are present after many cystoplasties and may be of no clinical significance. Failure because of a steep increase in the tonus limb is rare and usually the result of a technical error.

Gastrointestinal cystoplasty increases capacity and improves baseline pressure, but significant contractile activity can occur even after detubularization and reconfiguration of the intestinal segment. Urodynamic studies should be repeated in any patient who exhibits persistent incontinence, recurrent febrile infection, or new hydronephrosis. Patients and families should be told preoperatively to expect approximately a 0.5% to 10% failure rate in achieving a compliant noncontractile reservoir. Other morbidity is also potentially created by augmentation cystoplasty because bowel is not a perfect physiologic substitute for bladder; these complications are discussed in decreasing order of incidence.

COMPLICATIONS

Mucus Production

Because gastrointestinal segments maintain their intrinsic properties after incorporation into the urinary tract, mucus production by bowel mucosa continues after reconstruction. Canine experiments revealed that colonic segments produce more mucus than ileum does, and that stomach produces the least amount.[42] Most surgeons also have noted this pattern clinically and find that mucus is rarely problematic after gastrointestinal cystoplasty. Mucus production becomes more noticeable in the early postoperative period as the patient resumes oral intake. Production is also increased during urinary tract infection. Although some atrophy of ileal mucosa within the augmented bladder occurs eventually, no decrease in mucus production over time has been documented quantitatively.[43] Glandular atrophy in colonic segments is not evident histologically after long-term exposure to urine.[44]

Excessive mucus production or accumulation in the bladder can interfere with bladder emptying via CIC. Poor emptying may predispose the patient to urinary tract infection and stone formation. Routine saline irrigation of the bladder at the time of one catheterization each day and whenever drainage is obviously incomplete may help reduce the incidence of clinical problems related to mucus production.

Urinary Tract Infection

Urinary stasis, CIC, mucus production, and urinary pH changes all may contribute to a high incidence of bacteriuria after enterocystoplasty. Consistently sterile urine is found in some patients who void spontaneously and to completion after creation of an orthotopic neobladder, but bacteriuria is nearly universal in patients using CIC after augmentation.[45,46] Symptomatic urinary tract infection is less common, but the incidence depends on how carefully signs or symptoms are sought. All patients catheterizing to empty after augmentation should be told to expect that they will sometimes develop cystitis. At Indiana University, symptomatic lower urinary tract infection requiring treatment occurred in at least 22.7% of patients with ileocystoplasties, 17.3% of patients with sigmoid cystoplasties, and 8% of patients gastrointestinal cystoplasties. Febrile infections occurred within all groups in about 10% of patients.[32]

Treatment of asymptomatic bacteriuria in most patients performing CIC is typically not indicated except in the presence of a urea-splitting organism on culture. Bacteriuria is otherwise treated when it causes signs or symptoms, such as hematuria, discomfort with catheterization, suprapubic pain, incontinence, remarkably increased mucus production, or a foul odor. Treatment with a short course of oral or intravesical antibiotics is usually effective.

Calculi

Many potential factors influence the incidence of stone formation after augmentation cystoplasty, including urinary stasis; abnormal urine pH and citrate; bacteriuria; mucus production; and the presence of foreign bodies such as sutures, staples, or catheter fragments. Most calculi in this population are found in the bladder, although patients are also at increased risk for upper tract stones. Bladder calculi after enterocystoplasty have been reported in 12% to 50% of patients.[46-49] In the largest series, which reviewed 500 patients, bladder stones were found in 15% of patients, requiring 1.72 stone surgeries per patient. There was no statistically significant difference in stone occurrence in ileum versus colon. There were no stones in pure gastric augmented bladders.[38] Kronner and colleagues[49] also showed a statistically significant increase in stone risk with the additions of a bladder outlet procedure and a continent abdominal wall stoma to augmentation.

Most bladder stones in this setting are composed of struvite, and bacteriuria with urea-splitting organisms has been implicated in the etiology. Poor bladder emptying can play a role as well. Palmer and associates[48] recommend meticulous attention to emptying and daily bladder irrigations to remove nidi (mucus, crystals) for stone formation. Stones occur infrequently after gastrointestinal cystoplasty, affecting only 2% to 9% of patients in several series.[34,50,51] Stone formation after gastrointestinal cystoplasty is discouraged by the acidic environment and low incidence of mucus and infection. Most stones noted after gastrointestinal cystoplasty are actually uric acid in composition.

Calculi can be removed from the augmented bladder either endoscopically or by open cystolithotomy. In the series of Kronner and colleagues,[49] a higher stone recurrence rate was noted after cystolithotripsy (54% versus 33%) compared with open removal, although this difference did not reach statistical significance. Extracorporeal shock wave lithotripsy has not been used with good success after augmentation. Bladder irrigation with hemiacidrin may have a role in the dissolution of stone particles after treatment, but is not beneficial in treatment of intact stones.[47] Care must be taken to avoid magnesium intoxication from absorption if it is used.

Metabolic Complications

Since Ferris and Odel[52] noted profound electrolyte abnormalities in patients after ureterosigmoidostomy in 1949, the potential metabolic implications of incorporating bowel into the urinary tract have been recognized. The particular pattern of metabolic derangement varies depending on the segment of the gastrointestinal tract used for augmentation. Hyperchloremic metabolic acidosis is most common and generally associated with use of either ileum or colon, whereas gastric segments may cause hypochloremic metabolic alkalosis.

Hyperchloremic Metabolic Acidosis

When ileal or colonic segments of bowel are incorporated into the urinary tract, the mucosa retains its absorptive and secretory properties. Chloride ions are absorbed from the urine, and bicarbonate ions are secreted across the bowel lumen by an exchange mechanism. Ammonium, hydrogen ions, and organic acids are also readily reabsorbed by the bowel mucosa.[53] The extent of the electrolyte exchange depends not so much on whether ileum or colon is used, but more on the amount of intestinal surface area in contact with the urine and the time of exposure. Each patient has an element of acute and then chronic acid loading because of the absorption. The chronic acid load and secretion is buffered by the large amounts of ammonium produced and secreted by the distal renal tubular cells, a mechanism that can be lost with renal insufficiency. The intestinal mucosa readily reabsorbs the ammonium back from urine. This reabsorption of ammonium apparently contributes more to systemic acidosis after ureterosigmoidostomy or augmentation than does either the secretion of bicarbonate or the reabsorption of organic acids.[53]

After augmentation cystoplasty with ileum or colon, nearly all patients with normal renal function have some increase in serum chloride and decrease in bicarbonate from their preoperative level, although most of these values remain within the normal range.[33] Patients presenting with a significant hyperchloremic metabolic acidosis after augmentation cystoplasty in the face of normal renal function should be evaluated for poor bladder emptying. Arterial blood gas sampling might prove to be more effective in detecting subtle signs of acidosis than venous sampling.[54] When acidosis does occur, total body depletion of potassium and phosphate may be extreme despite normal serum levels.

Depletion of Bony Buffers

Because the normal renal mechanism for buffering a chronic acid load is disabled by reabsorption of ammonium across the intestinal patch, inorganic salts from bone are liberated as buffer. Bone demineralization and impaired growth can be shown in some rodents after urinary diversion despite the absence of significant systemic acidosis.[55] A similar potential concern for children after augmentation may exist; however, because most augmentations performed in children are done on children with myelodysplasia, documenting a causative effect on linear growth is difficult.

Gros and associates[56] evaluated growth patterns in children who underwent bladder augmentation for management of bladder exstrophy. The group with augmentation was compared with a group of age-matched and gender-matched controls without augmentation. In the augmentation group, 82% of the patients had a decrease in percentile height compared with their preoperative status. Overall, there was a 15% decrease in percentile height among patients undergoing augmentation; this number corresponded to a decrease of 1.5 inches from expected height. By comparison, 33% of patients not undergoing augmentation had impaired linear growth, but the group as a whole showed a net increase in percentile height.[56] Although the study included only a few patients, and did not consider any provision for familial growth patterns, the decrease in percentile height in the group with augmentation was troubling. Mingin and colleagues[57] in a well-done study did not show similar problems. All children with chronic metabolic acidosis after augmentation cystoplasty should be given oral alkaline therapy. The impact of subclinical acidosis in these patients may be underestimated, and better understanding of the issue is needed.

Absorption of Other Solutes

Reabsorption of other urinary solutes or drug metabolites may occur across the bowel mucosa and affect management of coexisting medical problems after cystoplasty. The extent of reabsorption depends on the time that the bowel is in contact with urine. Dilantin reabsorption after urinary diversion has required modification of the dosing regimen.[58] In addition, because the intestine readily reabsorbs glucose, urinary glucose spot checks in diabetic patients may yield misleading results.[59]

Hypokalemic and Hypochloremic Metabolic Alkalosis

Gastric mucosa remains secretory after gastrointestinal cystoplasty,[60] and secretion of hydrogen and chloride can result in hypochloremic metabolic alkalosis. Exposure to alkaline urine and stretching of the gastric patch with bladder filling likely stimulate further acid secretion. Serum chloride levels usually decrease and serum bicarbonate levels increase after gastrointestinal cystoplasty in patients with normal or compromised renal function.[26,61] Patients with renal insufficiency and preexisting metabolic acidosis potentially benefit most from such trends, and many are able to discontinue long-term alkalization therapy because of the acid secretion by the gastric patch.[34,61]

Acute problems with metabolic alkalosis can also occur because of the secretion. Acute metabolic alkalosis has usually occurred during a gastrointestinal illness with vomiting and poor oral intake and has been severe enough to require hospitalization in 3% to 24% of patients.[51,61,62] Renal insufficiency, the primary indication for use of stomach for augmentation, seems to predispose patients to more risk for metabolic alkalosis.[61] Patients with chronic or recurrent electrolyte abnormalities may require salt supplementation or H_2 blockade.[63,64] Inhibitors of the gastric mucosal H^+,K^+-ATPase pump (e.g., omeprazole) are warranted in cases refractory to other medical management.[63,65] Rarely, patients may require removal of the gastric segment or the addition of an ileal patch creating a composite urinary reservoir to counteract the existing electrolyte abnormalities.[63]

Aciduria and Hematuria-Dysuria Syndrome

Hematuria-dysuria syndrome is a complication unique to gastrointestinal cystoplasty, and the incidence has varied widely depending on how loosely the problem is defined and how carefully patients are questioned about it. Virtually every patient after gastrointestinal cystoplasty may have some sign of the problem if only to minor degree. The syndrome is characterized by some combination of bladder spasms, dysuria, suprapubic or urethral pain, gross hematuria, and excoriation of periurethral or perineal skin and is likely caused by irritation by the acidic urine.[66] Nearly 50% of patients may be troubled by the problems enough to complain or require treatment occasionally, including 68% of sensate (non-neuropathic) patients compared with only 25% of insensate neuropathic patients.[67] Incontinent patients seem to be more severely affected.[66] Not only may leakage of urine expose the skin to acidic fluids, but also failure of continence results in less dilution and buffering of the secreted acid. Except under distinct indications, gastrointestinal cystoplasty should be avoided in patients with normal sensation from the native bladder because of this syndrome.

When treatment of these signs or symptoms is required after gastrointestinal cystoplasty, adequate oral intake of fluids helps dilute the acid. Symptoms usually respond to H_2 blockers or H^+,K^+ ion pump inhibitors.[66] Treatment with oral agents or with bicarbonate bladder irrigations is particularly important during periods of catheter drainage or bladder defunctionalization because the exposure of urothelium to acid may be unbuffered at those times.[68] The potential impact of aciduria is emphasized by a report of ulceration and perforation in a defunctionalized gastrointestinal cystoplasty.[69]

Composite Reservoirs

The metabolic derangements created by stomach and ileum/colon in the urinary tract can be used to oppose each other,[70,71] and decrease the limitations of each segment alone in some patients. Composite continent reservoirs or augmentations have generally been done in very complex patients or patients requiring secondary augmentation for problems after primary cystoplasty with remarkably good results. Potential changes in serum electrolytes, including chloride and bicarbonate, and elevations in serum gastrin levels or signs of the hematuria-dysuria syndrome have not been noted.[70,71] Although the combination can achieve apparent metabolic neutrality, widespread use of composite augmentation for routine, primary cystoplasty is unlikely because it is cumbersome and requires two bowel anastomoses.

Spontaneous Bladder Perforation

Spontaneous perforation, although potentially lethal, was not readily recognized until well into experience with bladder augmentation, and represents one of the most concerning potential complications of augmentation cystoplasty. Early leaks along the enterovesical anastomosis are uncommon and likely represent delayed healing, a technical error, or an overzealous cystogram.[32] Late perforations occur within the bowel segment, usually near the enterovesical anastomosis, and represent a true failure of bowel as a urinary storage tissue. The pathophysiology of these perforations remains theoretical, but ischemia, trauma, adhesions, hyperreflexia, chronic overdistention, and infection all have been proposed as contributing factors.[72-77] There is a field effect of the offending factor because previous spontaneous bladder rupture is clearly a risk factor for repeat perforation.[32,78] Spontaneous perforation was literally never recognized in the era before routine bowel reconfiguration for cystoplasty.

Among the first 330 bladder augmentations at Indiana University, 32 spontaneous perforations occurred in 24 patients (7.3%). All of those 24 patients had high outlet resistance, whether native or surgically constructed. Perforation occurred in 16.5% of patients after sigmoid cystoplasty, accounting for 59% of all perforations. By comparison, the incidence of rupture after ileal cystoplasty or gastrointestinal cystoplasty was 4.5% and 8%.[78] This statistically significant increase in the risk of perforation associated with sigmoid augmentation is the opposite of that noted in some other large series, including the Boston Children's Hospital experience, in which perforation incidence was highest after use of ileum (9.3% versus 4.2% for sigmoid).[77] The latter series included fewer patients with a diagnosis of spina bifida. Because the findings have not been consistent across multiple large series, it is difficult to conclude that one segment is a greater risk in every patient population. In the first 500 patients at Indiana, 43 patients (8.6%) had bladder perforations; 87% were treated surgically, and 13% were managed conservatively.[38]

Patients may be critically ill at the time of presentation, and the event has been fatal. Signs and symptoms can be masked by impaired visceral sensation in neurogenic patients. The index of suspicion for rupture must be high, and antibiotics and catheter drainage should be instituted immediately while radiographic evaluation is performed. Computed tomographic cystography is the preferred diagnostic study because standard fluoroscopic cystograms have a 33% false-negative rate.[78] A large fluid collection next to the bladder may represent a positive finding even if no leakage of contrast fluid into it is shown.

The risk of fatal sepsis increases with delay in diagnosis and treatment, and a strong clinical suspicion of perforation should override a negative radiographic evaluation. Standard treatment for spontaneous bladder perforation is immediate exploratory laparotomy with débridement and closure of the perforation and copious irrigation of the peritoneal cavity. Externalization of a ventriculoperitoneal shunt, if present, may be necessary. Conservative management with parenteral antibiotics, catheter drainage, and serial examinations has been successful in some cases[38,79]; even some patients who do well in the short-term ultimately require surgical intervention.[78] One could never be criticized for operating immediately if rupture is suspected.

Malignancy

Development of adenocarcinoma at the ureterointestinal anastomosis site is another well-recognized complication of ureterosigmoidostomy.[80] The procedure creates a 7000-fold increase in the risk of developing adenocarcinoma of the colon after a mean latency period of 26 years.[81] Although the exact mechanism for tumor induction after urinary diversion is not well understood, carcinogenic substances may be produced by the admixture of urinary and fecal streams after ureterosigmoidostomy. *N*-nitroso compounds are found in that setting, and have been found in urine after augmentation cystoplasty and loop diversion.[82,83] Animal studies have revealed hyperplastic growth in various enteric segments after augmentation cystoplasty,[84-86] and tumors have been discovered anecdotally in humans after augmentation with either ileum or colon.[87] The earliest note of tumor formation was only 4 years after bladder augmentation.[88] Dysplasia and metaplasia of urothelium and adenocarcinoma or transitional cell carcinoma have been observed near the vesicoenteric anastomosis in humans.[89,90] Soergel and coworkers[91] reported three cases of transitional cell carcinoma after augmentation cystoplasty. They believed that intestinal cystoplasty was an independent risk factor for malignancy, noting a risk of 1.2% to 3.8%.

Because the latency for tumor formation after ureterosigmoidostomy is so lengthy, the long-term tumor risk after augmentation cystoplasty may be grossly underappreciated at this point. Yearly endoscopic evaluation of the augmented bladder for tumor surveillance beginning about 8 years after reconstruction seems prudent, although the efficacy of such a program is not proven. Urinary cytology or flow cytometry may ultimately be useful in surveillance as well.

Problems with Pregnancy

As patients with augmentation cystoplasties mature into childbearing years, it becomes clear that our understanding of the outcome of bladder augmentation during and after pregnancy is based on poorly reported, anecdotal experience. Loss of an augmentation because of mechanical effects on the pedicle has not been reported. Usually, the pedicle is displaced laterally by the enlarged uterus at the time of cesarean section, but no apparent stretching of the pedicle is observed.[92,93] Pregnancy may hormonally affect the mesentery as it does other tissues and allow the necessary expansion to accommodate the uterus. If cesarean section is required in a patient with augmentation cystoplasty and continent stomas, a pediatric urologist familiar with the anatomy should be present to protect the augmented bladder and vascular pedicle.

As previously noted, bacteriuria is very common after augmentation cystoplasty. The risk of pyelonephritis is increased with bacteriuria during pregnancy, and preterm labor is a potential consequence. Use of nonteratogenic prophylactic antibiotics may be prudent in such patients. Spontaneous vaginal delivery is unlikely to be more problematic as long as delivery progresses appropriately, and the bladder is kept empty. Patients who have undergone major reconstruction of the bladder outlet to achieve continence may best be delivered by cesarean section, however, to avoid any injury to the surgical repair or to the surrounding supportive tissues.

ALTERNATIVES TO GASTROINTESTINAL CYSTOPLASTY

As noted earlier, gastrointestinal cystoplasties can result in significant complications even when a good technical result and compliant reservoir are achieved. Although early and aggressive treatment of primary bladder dysfunction may prove effective at decreasing the need for surgical augmentation of the bladder, alternatives to gastrointestinal cystoplasty have been developed in an effort to decrease morbidity for a patient who still fails conservative measures. The alternatives, in principle, attempt to provide a compliant reservoir of adequate size with urothelial lining.[94] Further work and experience in the area are warranted.

Autoaugmentation

Cartwright and Snow[95] proposed that excision of the muscularis of the bladder dome leaving the urothelium to bulge in a manner similar to a diverticulum could improve bladder dynamics. This urothelial bulge, if persistent, could theoretically augment capacity, decrease contractility, and improve compliance.

Technique

Patients should undergo the same bowel preparation as described earlier for intestinal cystoplasty because if capacity is not markedly improved after detrusorectomy, intestinal cystoplasty should be performed.[96] The bladder is distended with saline and exposed through a lower abdominal incision. Although it has been shown that vesicomyotomy (incision) achieves similar results to vesicomyectomy (resection), resection of the bladder muscle is generally favored.[97,98] A midline bladder incision is made to the level of the lamina propria with a needle-tipped electrode, and the musculature is elevated from the urothelium with either a hemostat or Kitner dissector on either side (Fig. 57-7).

At least 50% of the detrusor muscle should be excised according to Cartwright and Snow.[95] Fixation of the remaining bladder muscle bilaterally may aid in preservation of the diverticulum. These authors recommend measurement of compliance and capacity after resection. If both are significantly improved, a suprapubic tube is placed through the

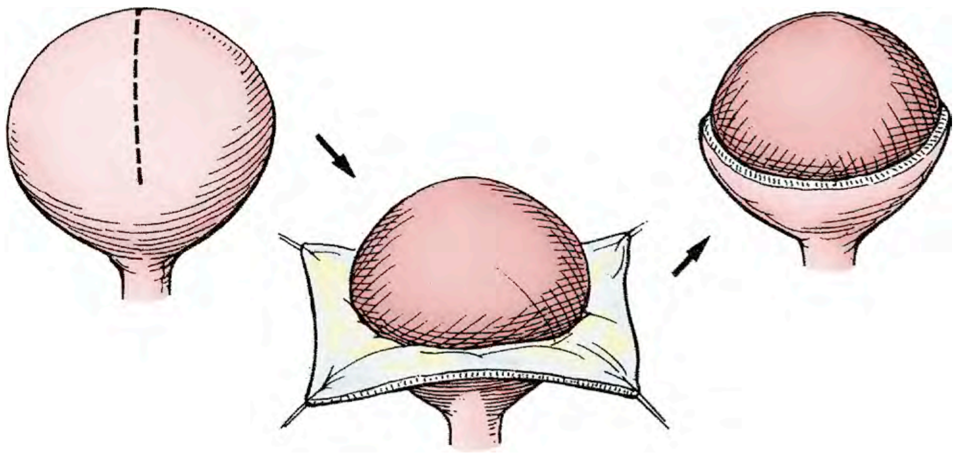

Figure 57-7 Autoaugmentation. Midline bladder incision to the urothelium. Muscle is separated from the urothelium, and the detrusor is excised leaving the urothelium to bulge as an "augmentation segment." (From Rink RC. Bladder augmentation: options, outcome, future. *Urol Clin North Am.* 1999;26:111-123.)

remaining bladder musculature, and the drainage tubing is elevated to a height of 15 cm to keep the urothelium expanded in the early postoperative period. Alternatively, an intravesical balloon may be temporarily placed to keep the bladder distended. If there is no improvement in compliance and capacity, intestinal cystoplasty should be performed instead.

Results

The results of autoaugmentation have been mixed. Some patients have shown clinical improvement without significant objective urodynamic improvement. Any increase in capacity may be inadequate.[99] Landa and Moorhead[100] reported that the increase in volume is "modest at best." Despite several small series reporting good results in pediatric patients,[101,102] Stothers and coworkers[98] noted an increase in capacity by only 15% to 70%. In a combined series of 25 patients from two groups, a good clinical result was achieved in only 52% of patients, with 28% having acceptable outcomes and 20% having poor outcomes.[96] Experimentally, fibrosis and thickening around the urothelium are demonstrable and lead to a decrease in the surface area of the diverticulum by 50% at 12 weeks[97]; these changes may contribute to the marginal clinical results. Use in adults with hyperreflexia but good capacity, a rare situation in children, has been reported to achieve good results,[103,104] but Milam (DF Milam, personal communication, 2000) reported that nearly 50% of patients achieving a good result initially for hyperreflexia fail on long-term follow-up.

Ureterocystoplasty

Ureter is an ideal tissue for bladder augmentation if enough is present. It has long been recognized that a refluxing megaureter can behave as an effective pressure "pop-off" for an abnormal bladder.[105] Early reports of ureterocystoplasty described use of massively dilated ureters subtending a nonfunctioning or poorly functioning kidney. Initially, only ureter was used[106,107]; more experience showed that, with care, the renal pelvis could be used in some cases with the ureter.[108-110]

Technique

A single midline intraperitoneal approach can be used, but several groups have reported the use of separate extraperitoneal flank and suprapubic incisions.[107,110,111] In either case, a nephrectomy is usually performed with care to preserve the renal pelvic and upper ureteral blood supply that arises medially. During ureteral mobilization, all ureteral adventitia is swept from the peritoneum toward the ureter. The distal ureteral blood supply is carefully preserved as it enters laterally. The bladder is opened in the sagittal plane with the posterior incision carried from the midline through the ipsilateral ureteral orifice (Fig. 57-8A and B).

Alternatively in cases with a large ureter, similar results can be obtained by leaving the last 2 to 3 cm of the ureter intact to avoid injury to the ureteral blood supply and the superior vesical artery.[112] Either way, the ureter is incised longitudinally away from its blood supply and major adventitial vessels and then reconfigured to create as spherical a reservoir as possible when anastomosed to the bladder (Fig. 57-8C). The anastomoses are performed using absorbable suture, taking care to invert mucosa as described with routine augmentation cystoplasty. Likewise, a suprapubic tube is left indwelling through the native bladder for 3 weeks during healing.

There are reports of the use of a portion of the distal ureter from a functioning kidney with subsequent reimplantation or transureteroureterostomy of the proximal ureter.[113,114] The potential to expand a normal-caliber ureter has been addressed experimentally and holds promise for human use.[115,116] Ikeguchi and associates,[117] using a ureteral tissue expander over a stent in pigs, obtained ureteral volumes of 150 to 1000 mL.

Results

Landau and colleagues[118] first compared ureterocystoplasty with ileocystoplasty in age-matched, diagnosis-matched patients, and found the bladder capacity to average 417 mL after using ureter and 381 mL after using ileum. Bladder volumes at 30 cm H_2O were 413 mL for ureter and 380 mL for ileum. In several subsequent series, the results were good, and complications were rare.[119,120] In contrast, Gonzalez[121] reported that one quarter of his patients with posterior urethral valves experienced failure after ureterocystoplasty owing to their large urine output. In a multicenter experience, Husmann and associates[122] also noted problems, particularly if the ureter used was not greater than 1.5 cm in diameter on preoperative imaging.

Ureterocystoplasty works well to achieve the goals of augmentation and can be considered as the augmentation of

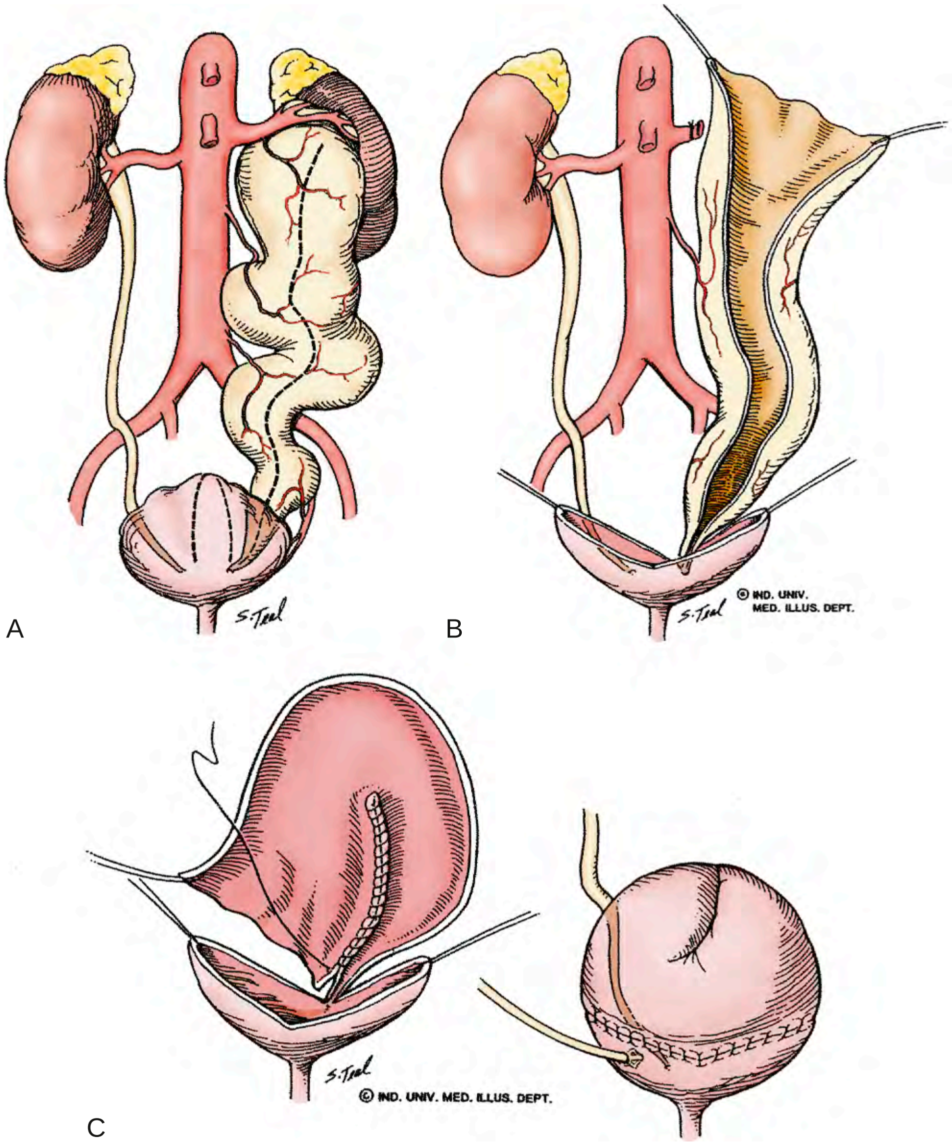
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Figure 57-8 Ureterocystoplasty. **A,** Bladder is bivalved in the sagittal plane and to the ureteral orifice. **B,** Blood supply to the ureter is preserved, and the kidney is removed. The ureter is detubularized along its length. **C,** The megaureter remains attached to the bladder and is reconfigured for a spherical reservoir. (**A,** From Rink RC, Adams MC. Augmentation cystoplasty. In: Marshall FF, ed. *Textbook of Operative Urology.* Philadelphia: Saunders; 1996:916. B and C, © Indiana University Medical Illustration Department.)

choice if enough ureter is present. The obvious disadvantage is that with proper early care in neurogenic and exstrophy populations, one should not often find a child with a massively dilated ureter and a nonfunctioning kidney. With further work on expanding normal-caliber ureters, perhaps the patient population benefiting from ureterocystoplasty can be increased.

Seromuscular Segments (with Urothelial Lining)

The use of seromuscular segments for augmentation cystoplasty dates back to work by Shoemaker and Marucci in the 1950s.[123] Most experience with seromuscular segments alone, whether facing the bladder lumen or reversed, has led to contracture even when slow re-epithelialization with urothelium occurred.[124-127] More recently, demucosalized segments of sigmoid colon and stomach have been placed over intact urothelium created using techniques similar to autoaugmentation. Gonzalez and colleagues[128] have used demucosalized sigmoid colon over urothelium. In their early clinical experience with seromuscular colocystoplasty lined with urothelium (Fig. 57-9), bladder capacity increased 2.4-fold in 14 of 16 patients, with end filling pressures decreasing from 51.6 to 27.7 cm H_2O.[128] The remaining two patients experienced failure and required ileocystoplasty. Ten patients eventually underwent bladder biopsy; in one, urothelium with islands of colonic mucosa was noted, and in two others only colonic mucosa was found. These authors and others[129,130] have suggested that preservation of the entire submucosa on the demucosalized enteric segment is important in preventing contracture. Dewan and colleagues[131] noted, however, that the inner portion of the submucosa and muscular mucosa must be removed to prevent enteric mucosal regrowth.

The use of demucosalized stomach over urothelium was reported initially by Dewan and Byard[132] in sheep and humans. Several other reports of early work with the

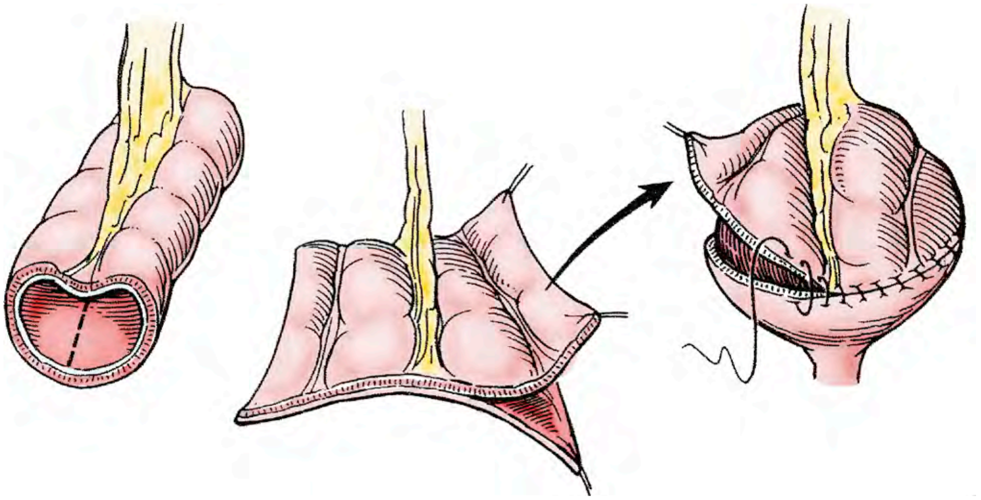

Figure 57-9 Seromuscular colocystoplasty plus autoaugmentation. Sigmoid colon is opened on its antimesenteric border, and the mucosal lining is removed. The remaining seromuscular colonic segment covers the autoaugmented bladder. (From Rink RC. Bladder augmentation: options, outcome, future. *Urol Clin North Am.* 1999;26:111-123.)

technique were encouraging.[133-135] Results reported by Carr and associates[136] were less optimistic. Of their 13 patients who underwent the procedure, only 5 children had a good clinical result, 4 had a fair outcome, and 4 had poor results. They noted that stromal-epithelial interactions are poorly understood at this time, and that results were inadequate to recommend routine use. Even with short follow-up, reoperation rates have been higher, whether using colon or stomach, than for routine intestinal cystoplasty.[41,128,136] Refinements in technique may optimize the results by minimizing the risks of graft contracture and intestinal mucosal regrowth. Such regrowth must be prevented to suggest that these segments may decrease morbidity for patients. More experience and longer follow-up should help to determine the role and efficacy of demucosalized segments, and whether the increased time of surgery is warranted.

Tissue Engineering

Early efforts to create an "artificial" bladder were largely unsuccessful and have been well reviewed by Gleeson and Griffith.[137] More recently, major advances made in the area of tissue regeneration and engineering give promise of clinical benefit. Some such work revolves around the use of biodegradable scaffolds for bladder wall growth either in vivo or in vitro. So-called unseeded regeneration involves use of a biodegradable scaffold sewn to the native bladder as with any other segment for augmentation, which is then modeled in place by the body. Using pig small intestine submucosa, Kropp and colleagues[138] showed regeneration of urothelium and muscle that behave histologically and functionally as bladder.[139-141] How regenerated tissue will function, particularly in a bladder with abnormal innervation, remains to be seen. Several other groups have used acellular matrix or grafts as the scaffold with similar early bladder regeneration.[142,143]

Atala and colleagues[144,145] showed that bladder tissue can be harvested, grown, and expanded in vitro for later bladder augmentation. Growth of all bladder layers in this "seeded" technique has been shown, and the engineered tissue has been used anecdotally.[146-149] Although these techniques hold great promise,[149] much is still to be learned, and routine clinical use remains a future possibility.

Catheterizable Channels

Nearly every child who undergoes major urinary tract reconstruction with augmentation cystoplasty is committed to a lifetime of CIC. Catheterization must be accepted into the lifestyle and daily routine of patients and their families, and surgical innovations may allow earlier independence for patients by providing easier or more reliable access to the bladder. A major contribution occurred when Mitrofanoff[150] introduced the principle of a continent catheterizable abdominal wall stoma in 1980, and since the initial description using appendix, various tissues, including reconfigured or tapered intestinal segments, ureter, tubularized bladder, and fallopian tube, have been used in a similar fashion. Detailed descriptions of several of these techniques are found elsewhere in this textbook, but with each, a straight, uniformly tubular structure is brought to the abdominal wall in a manner to provide easy catheterization. Tunneling of the structure submucosally into the bladder or reservoir creates continence. Despite potential complications with catheterizable channels, of which stomal stenosis is the most common,[151] their intimate association with augmentation cystoplasty is clear. The long-term results of bladder augmentation depends on the routine use of CIC for almost all patients; an adjunctive means of catheterization that is easy and reliable may improve those results.

The complete needs of the patient and family should be appreciated before surgical reconstruction is undertaken. If catheterizable channels are needed to empty the bladder regularly or for bowel irrigations and fecal continence, it is beneficial to recognize these needs initially and to create the channels at the time of augmentation cystoplasty. Successive reconstructive procedures become more difficult for the surgeon and result in more morbidity for the patient.

CONCLUSION

Augmentation cystoplasty has been a remarkable advance for children with small-capacity, poorly compliant bladders. It provides an adequate urinary reservoir for almost every patient when necessary. It has resulted in an entirely new set of urologic complications, however; some are common but a nuisance, whereas others are potentially lethal but rare. Efforts should continue to understand underlying bladder dysfunction and treatment better to decrease the need for bladder augmentation. Experience with alternative surgical techniques and research in tissue engineering should continue to provide a urothelium-lined reservoir or bladder. Surgeons interested in complex bladder reconstruction must familiarize themselves with such advances, but for now should be comfortable and capable with each kind of augmentation cystoplasty. No single technique or segment is best for every patient. Each child is unique, and the best results are achieved when the surgical procedure used is chosen based on the particular needs of that patient and not any bias of the surgeon.

Finally, regardless of the technique used, the ultimate result depends on a team effort. Patient selection and education, and family and patient motivation are crucial factors. All individuals involved must understand that success requires a lifelong commitment to good care.

REFERENCES

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SECTION 2

SURGERY FOR INCONTINENCE

CHAPTER 58

BLADDER OUTLET SURGERY FOR CONGENITAL INCONTINENCE

Jack S. Elder and Joao Luiz Pippi Salle

Surgical treatment of urinary incontinence in children is a difficult problem for urologists. Urinary incontinence associated with spina bifida and bladder exstrophy is severe, and its treatment remains a challenge. Affected individuals have fragile self-esteem and are frequently stigmatized by society.[1] Incontinent patients are often underachievers at school and may be denied employment opportunities as young adults.[2,3]

In children with neuropathic urinary incontinence, clean intermittent self-catheterization (CIC), as popularized by Lapides and colleagues,[4] in conjunction with pharmacologic manipulation with anticholinergics (e.g., oxybutynin, hyoscyamine, or tolterodine), produces continence in a variable proportion of patients. Success rates of 40% to 88% with this approach have been reported.[5-11] Consequently, many patients remain incontinent despite efforts with conservative management and require a surgical approach to achieve dryness. Many patients with a neuropathic bladder have decreased bladder compliance and are wet despite having adequate urethral resistance. Most of these patients achieve dryness with bladder augmentation alone and CIC.[12]

PREOPERATIVE EVALUATION

Lower and upper urinary tract function should be thoroughly assessed. A voiding cystourethrogram is necessary to assess bladder capacity, shape, and trabeculation, and to determine whether vesicoureteral reflux is present. Urodynamic studies of the bladder include a cystometrogram to assess bladder capacity and to identify detrusor hyperreflexia. The predicted normal bladder capacity is most easily determined by the following formula: bladder capacity (ounces) = age (years) + 2. In children with a neuropathic bladder, bladder capacity is often reduced. The peak detrusor pressure may be inaccurately measured as low in the presence of high-grade reflux, and the bladder capacity may be inaccurately identified as low if the outlet resistance is so low that fluid leaks out of the bladder before it fills. Occluding the bladder neck with a catheter may ameliorate this problem. The ideal method of assessing the lower urinary tract is with videourodynamics.

The bladder outlet can be measured in several ways, including leak point pressure and electromyography. No criteria predict with 100% accuracy whether the bladder outlet is intact or incompetent. In the past, the urethral pressure profile was used, but with experience it has not provided a reliably accurate assessment. The Valsalva leak point pressure also has been reported to be helpful because it simulates circumstances that cause incontinence, but it has been unreliable in children. The sphincter is easiest to assess with videourodynamics, although this diagnostic modality is unavailable at some institutions.

At present, the bladder outlet resistance may be assumed to be insufficient if the bladder neck is open on fluoroscopy, if sphincter denervation is identified on electromyography, or if the leak point pressure is less than 30 to 40 cm H_2O. Some children have poor bladder compliance and a borderline leak point pressure. In this group of patients, it is difficult to predict from the urodynamic data whether bladder augmentation alone or combined with a procedure to increase bladder outlet resistance will be necessary for continence.[13,14] In such cases, the urodynamic evaluation should be performed in two stages: The test is initially performed in the routine manner and then repeated with a balloon catheter occluding the bladder neck. This maneuver offers a better challenge for bladder distention and allows more accurate evaluation of compliance.[15]

The upper urinary tract may be assessed in many ways, including a renal ultrasound, excretory urography, computed tomography (CT) scan, or renal scintigraphy. The goal is to assess whether there are two kidneys, and whether they are normal in appearance and function. Many children undergoing lower urinary tract surgery have upper tract changes, such as urolithiasis, hydronephrosis, or renal scarring.

The need for concurrent bladder augmentation during surgical procedures that increase urethral resistance has been discussed previously. Levesque and associates[16] performed bladder augmentation when urodynamic evaluation showed detrusor filling pressures greater than 20 cm H_2O at 50% or less of predicted bladder capacity for age. De Badiola and coworkers[17] recommended simultaneous augmentation only in patients with a preoperative bladder capacity of less than 60% of expected capacity for age, and a compliance of less than 2 mL/cm H_2O. Barrett and colleagues[18] stated that patients with an increase of 15 cm H_2O per 100-mL volume increase should undergo simultaneous bladder augmentation with artificial urinary sphincter (AUS) implantation.[18] More recently, Kronner and associates[19] failed to show any urodynamic parameters that could predict the need for simultaneous bladder augmentation with AUS. Some patients with preoperative large, compliant bladders required augmentation later on, and conversely, some patients with small, less compliant bladders did not.

Despite many efforts to evaluate bladder outlet resistance, many cases remain in which the results are difficult to interpret, and the need for associated bladder augmentation with procedures to enhance outlet resistance is unclear.

Although not universally accepted, the static urethral pressure profile performed in the standard manner provides the initial baseline from which to gauge the success of any subsequent treatment.[20] It allows monitoring of urethral pressures continuously throughout filling and emptying of the bladder, obtaining a true dynamic measure of urethral and bladder neck function, and effectiveness of transmitted abdominal pressure.

SELECTION OF SURGICAL TECHNIQUE

Before considering the technical aspects of bladder outlet/urethral reconstruction, the importance of careful patient selection must be stressed. In most cases, a satisfactory outcome depends on the continuing commitment of the patient or, in younger children, the parents. Careful preoperative assessment is required to evaluate a patient's motivation and intelligence, and the degree of manual dexterity needed to perform CIC. Patients confined to wheelchairs may have difficulty accessing the genitalia for self-catheterization and may require an easier route to the bladder, which can be created by fashioning a catheterizable stoma to the abdominal wall (Mitrofanoff procedure).[21] Several procedures to increase urethral resistance have been described in the decades since Young first addressed the subject.[22] In children with a neuropathic bladder, the possibility of intermittent bladder emptying using CIC has given rise to a variety of procedures for reconstruction of the bladder outlet that provide continence, but, with a few exceptions, do not allow volitional voiding.

The ideal surgical technique to correct urinary incontinence should fulfill the following criteria: (1) use the patient's own tissue, (2) use a minimal amount of bladder tissue, (3) be durable and efficacious, and (4) allow easy access to the bladder through catheterization. Surgical procedures to achieve urinary continence are dictated by functional and anatomic deficiencies, and by the ultimate goal of either continence (with normal voiding) or dryness (dependent on CIC). Construction of a functional urethra allowing normal voiding is rare in children with a neuropathic bladder. Optimistic series reported spontaneous voiding in 5 of 19 patients (25%) who achieved continence in a group of 32 patients with a neuropathic bladder treated with AUS observed for 15 years.[23,24] Based on these data, it is fair to assume that most patients with neuropathic bladder need intermittent emptying by catheterization after increasing bladder outlet resistance, and any surgical technique aiming to achieve this goal should consider this aspect.

Surgical techniques for the treatment of urinary incontinence are based on the following basic principles:

1. Urethral lengthening procedures that produce an increase in hydraulic resistance, making a narrow and long urethral tube (Young-Dees-Leadbetter [YDL] technique and its modifications)
2. Construction of flap-valve mechanisms that produce a progressive increase in urethral resistance as the bladder or reservoirs become filled (Kropp procedure and other variations)
3. Suspension and external compression of the urethra (AUS, fascial slings)
4. Periurethral injection of bulking agents (increasing urethral resistance by narrowing urethral lumen)
5. Bladder neck closure

This chapter describes only bladder neck reconstructive procedures. The use of the AUS and injection techniques are discussed in other chapters (see Chapter 60).

YOUNG-DEES-LEADBETTER PROCEDURE

Surgical techniques for bladder neck reconstruction were initially described by Young in 1922,[22] and were later modified by Dees in 1949[25] and Leadbetter in 1964.[26] The YDL technique is often used in pediatric reconstructive surgery, especially in cases with normal bladder innervation, such as bladder exstrophy and epispadias, in which continence rates of 70% to 86% have been reported in large series.[27-29]

Surgical Technique

Bladder neck reconstruction is begun by placing the patient in a hyperextended position whenever possible because this may facilitate exposure of the bladder neck. The anterior bladder wall is approached with a longitudinal midline incision starting at the beginning of the urethra. A 12- to 14-mm-wide strip of mucosa is outlined in the midline trigonal area, starting at the proximal urethra. It is important to begin lengthening as far into the urethra as possible to avoid formation of an hourglass deformity, often seen in cases of failed YDL technique. The deep position of the proximal urethra makes this part of the procedure difficult, but one must pay attention to this technical detail to avoid failure.

The mucosa lateral to the edge of the strips is removed, creating triangular areas of denuded detrusor. The ureteral orifices are often located in this area and need to be reimplanted higher in the posterior bladder wall in a cross-trigonal fashion. The isolated mucosal strip is tubularized using running absorbable sutures over an 8F silicone stent. In difficult cases, additional exposure can be obtained by splitting the pubic symphysis, by either cutting through it or removing a wedge of bone and cartilage to expose the bladder neck and proximal urethra entirely.[30]

One of the sides of the detrusor muscle is cut along the horizontal edge of the denuded mucosa and is used to wrap around the neourethra in a pants-over-vest manner. A similar maneuver is done with the contralateral side of the detrusor, which is then brought around and sutured over the outer surface of the first flap, providing increased resistance at the new bladder neck. The neourethra should be at least 3 to 4 cm long to provide significant urethral resistance.

The anterior bladder wall is closed in two layers, starting at the beginning of the new bladder neck and extending up to the dome. The muscle layer of the neourethra and the new bladder neck is sutured to the undersurface of the pubic symphysis, creating urethral suspension. This technical step is important for maintaining the neourethra in an intra-abdominal position and for buttressing it against the undersurface of the pubis to help prevent stress incontinence. In pubertal or postpubertal boys, this last maneuver may be difficult to accomplish because of the growth of the prostate and its posterior attachments. Suspending the urethra may be easier when attempts are made to free some of these posterior attachments of the prostate.

Results

The use of the YDL technique for correction of neuropathic incontinence has not reached the same popularity as it has in children with exstrophy/epispadias, and there have been few reports with significant patient numbers. In 1987, Rink and Mitchell[7] reported an initial success rate of only 57% in 26 patients who ultimately achieved dryness after several additional continence procedures. Similar success rates were reported by Tanagho in 1981,[31] Arap and coworkers in 1988,[32] and Johnson and associates in 1988.[8]

Donnahoo and colleagues[33] reported further experience of Rink and Mitchell's 38 patients who underwent the YDL procedure for treatment of neuropathic incontinence. Twenty-three of 38 patients (60.5%) achieved total continence, and 3 (8%) achieved partial continence after the initial repair. Bladder augmentation was required in 35 patients (92%), and perforation of the augmented bladder occurred in 5 patients (14%). Four patients (10.5%) had significant difficulty with catheterization and required additional intervention. Similar experiences have been reported by others with difficult catheterization after YDL procedure, and special maneuvers to facilitate catheterization have been described.[13,34]

Attempting to stabilize the repair, Mitchell and Rink described a technique of wrapping the tubularized bladder neck with a silicone sheath.[35] The same group reported long-term follow-up with an unacceptably high complication rate (erosion, infection), and they concluded that wrapping with a silicone sheath should not be attempted.[36] This opinion is not shared, however, by Quimby and coworkers.[37] They initially had many failures with a similar technique, but achieved success using a thin, non-reinforced silicone sheath with a layer of omentum between the bladder and the sheath.[37] Quimby and coworkers believe that using the non-reinforced, thin silicone sheath with the addition of omentum decreases the erosion rate a nd improves the results. They currently reserve the use of the silicone sheath placement, however, for a small subset of patients who are most likely to benefit from subsequent AUS placement. In these cases, the removal of silicone facilitates placement of the AUS.[37] Besides difficulty with catheterization, another drawback of the YDL procedure is the significant loss of bladder capacity and the need to reimplant the ureters superiorly.[20]

MODIFICATIONS OF THE YOUNG-DEES-LEADBETTER PROCEDURE

Several groups have reported modifications of the YDL procedure. In 1993, Jones and associates[38] reported their modification of the original YDL bladder repair with improved results in terms of continence and associated morbidity. Most patients in this group experienced incontinence secondary to exstrophy and epispadias. This modification is initiated by a transverse incision through the anterior half of the proximal urethra. The incision is extended cephalad along the posterolateral proximal urethra, then cephalad along the posterior bladder wall to the ureteric orifices bilaterally. The incision is full thickness.

Exposure of the interior bladder is gained by gentle retraction as the incision is elongated. The ureters are reimplanted by either a Cohen or a Politano-Leadbetter technique. When the ureters are reimplanted, the urethra is tubularized using a two-layer running suture. Interrupted sutures occasionally also are used to ensure that the muscularis closure is tight. The neourethra is constructed over a catheter. A 5F Silastic catheter is left indwelling for the immediate postoperative period. If a sling or suspension of the urethra is made, it is usually done immediately after this closure. The bladder is then closed vertically in the midline. The original aspect of the transverse urethral incision is now located high on the bladder dome.

In the original report, 11 of 47 patients had neuropathic incontinence, and in this group, dryness and significant improvement were achieved in 64% (dryness) and 18% (significant improvement) of patients. Only three of these patients underwent the modified YDL procedure. It is difficult to draw conclusions with such small numbers of patients. The use of this modification in patients with exstrophy/epispadias complex was promising; however, whether similar positive results can be achieved in patients with neuropathic incontinence is unknown.

Subsequently, Mitchell modified this bladder neck reconstruction further by creating a demucosalized muscular pedicle flap and wrapping it around the bladder neck reconstruction.[39] Eight patients underwent the procedure, all of whom had exstrophy/epispadias, and all were continent.

Koyle[40] reported a modification of the YDL procedure for neuropathic incontinence on the basis of Rink's continent vesicostomy procedure. It combined intertrigonal posterior mucosal tubularization with construction of an intravesical neourethra, which works as a one-way flap valve, termed the Ppork procedure (or reverse Kropp). After the bladder is opened, each ureter is cannulated with a 5F or 8F feeding tube, and these are then sutured in place. This allows the surgeon to apply lateral traction on the ureters. If the measured distance between the two ureteral orifices is larger than 1.2 cm, the procedure can be applied. When the distance is shorter than 1.2 cm, another type of bladder neck repair should be used.

The bladder is opened further through the bladder neck. Parallel lateral incisions are made, beginning on either side of the bladder neck and extending cranially (1.5 to 2 cm above) and medially (0.1 cm on each side) to the ureters. This leaves an intertrigonal, posteriorly based mucosal island that is 1 cm wide and that extends 1.5 to 2 cm above the ureters. This mucosal island is tubularized using a two-layer closure, such as a Thiersch-Duplay urethroplasty. Deep interrupted sutures (usually one or two) are placed in the muscle medial to each ureter and are tied in the midline, advancing both ureters medially in the fashion of Gil-Vernet. Reimplanting the ureters in a more formal manner is rarely, if ever, necessary. The mucosa lateral to the extended urethra/bladder neck is undermined and then closed over the tube to complete the flap-valve concept.

Because of the construction of a flap valve, bladder emptying requires CIC, and an appendicovesicostomy (Mitrofanoff) was performed in all patients. Although catheterization did not seem to be a major problem, most patients preferred to be catheterized via the supravesical route. A technical point of concern is the overlapping of the two mucosal suture lines, which theoretically could enhance chances of fistula formation. Koyle[40] reported a continence rate of 82%, however, which makes this technique an attractive alternative to surgical treatment of neuropathic incontinence.

Similar techniques have been reported by Demirbilek and Atayurt[41] for patients with bladder exstrophy. In their experience, all patients underwent simultaneous bladder augmentation, and most patients were able to have volitional voiding, which in our experience is an extremely rare event in patients with augmented bladders.

BLADDER NECK CINCH/WRAP PROCEDURES

In 1990, Koff[42] described a bladder neck wrap procedure creating a demucosalized bladder muscle flap and wrapping the reconstructed urethra in children with bladder exstrophy. In 2002, Mingin and colleagues[43] described a modified rectus/pyramidalis myofascial sling based on the Goebel-Frangenheim-Stoeckel procedure.

Surgical Technique

A pedicle 2 cm × 8 to 10 cm in girls or 2 cm × 12 to 14 cm in boys consisting of rectus abdominis and pyramidalis muscle with overlying fascia is raised parallel to the midline, taking care to preserve the blood supply via the distal pubic attachments. The flap is doubly looped beneath the urethrovesical junction and sutured to the contralateral rectus sheath using a nonabsorbable suture. Sufficient tension is applied to coapt the bladder neck, while allowing for easy placement of a urethral catheter. The occlusive effect of the sling is assessed during surgery by filling the bladder and varying the tension on the sling until urethral urine leakage ceases. Augmentation cystoplasty and ureteric reimplantation were used when necessary, before suturing the rectus flap to the other side.

Urethral catheterization was maintained for 5 to 10 days after surgery; a suprapubic cystotomy was placed for 2 to 3 weeks when bladder augmentation is combined with sling suspension. Urethral catheterization was instituted 10 days after surgery if the sling was the only procedure; if the bladder was augmented, urethral catheterization was begun after clamping the suprapubic tube. Of 37 patients with a neuropathic bladder, the bladder was augmented in 33, and 34 (92%) were dry between catheterizations. Using a similar technique, with minimum 2-year follow-up, Albouy and associates[44] reported that 13 of 14 were continent; all of their patients also underwent augmentation enterocystoplasty.

A similar concept using rectus fascia has been reported by several groups.[45,46] A 1 to 1.5 cm × 6 to 7 cm strip of anterior rectus is harvested. After a concomitant procedure such as ureteral reimplantation or augmentation or both, the fascial strip is placed circumferentially around the bladder neck. A vertical slit is made 1 cm from one end of the strip. The opposite free end is passed through the slit and "cinched" snugly around the bladder neck. The wrap is secured to itself at the point of passage through the slit with 2-0 polydioxanone to prevent slippage. The free end is secured to the symphysis or rectus fascia, elevating the bladder neck and resulting in 360-degree compression of the bladder neck. In a series of 15 patients, Bugg and Joseph[46] reported a 60% success rate. Using a similar technique, Walker[47] has had slightly better success.

KROPP PROCEDURE

In 1986, Kropp and Angwafo[48] reported a creative procedure for the treatment of total urinary incontinence. This procedure consists of performing urethral lengthening with a tubularized anterior bladder wall flap, which is reimplanted in the posterior intertrigonal area, creating a one-way valve mechanism similar to the antireflux mechanism procedures used for correction of vesicoureteral reflux. Increases in intravesical pressure are transmitted to the submucosal urethral tube, increasing closure pressure and preventing incontinence.

Surgical success is based on the Mitrofanoff procedure and results in an effective one-way flap valve and a completely retentive patient who requires CIC for bladder emptying. It is mandatory that the patient or family or both be compliant and trained to perform catheterization routinely. As previously discussed, the need of simultaneous bladder augmentation is based on a provocative urodynamic evaluation using a balloon catheter to occlude the bladder neck to avoid leakage during the filling phase of the study. Kropp[49] has advised the same maneuver when performing a cystogram to evaluate the presence of vesicoureteral reflux and the need for reimplantation.

Surgical Technique

The patient is placed supine, with the sacrum over the kidney rest, which can be elevated to increase exposure of the bladder neck and proximal urethra. An appropriately sized Foley catheter is passed and kept sterile so that it can be accessible during the procedure. A suprapubic incision is made to expose the bladder neck and proximal urethra. The bladder is distended, and the bladder neck is identified by the palpation of the Foley balloon. From the bladder neck, a 5- to 7-cm × 2- to 2.5-cm strip of anterior bladder wall is outlined (Fig. 58-1A). The bladder is opened, and both ureteral orifices are identified and catheterized. The junction of the trigone and the bladder neck is identified from within, and the mucosa and superficial muscle are incised, beginning at the 6-o'clock position at the bladder neck and carrying this incision upward on either side of the bladder neck to meet the previous incision (see Fig. 58-1B).

In Kropp's original description, the remainder of the bladder neck is separated in the midline, and the plane of cleavage between the vagina (or seminal vesicles) and the bladder neck is identified. It is important to ensure that the one-layer suturing of the tubularized bladder strip starts precisely at the bladder neck and continues upward. It may occasionally be necessary to excise a V-shaped wedge of posterior bladder neck to make tubularization easier. The last 1 to 2 cm is closed with interrupted sutures in the event that the end of the tube has to be trimmed. If the tube is made too long, it can reach the area of the dome and kink when the bladder is full, making catheterization difficult (see Fig. 58-1C). If reflux is present, the ureters should be dissected free from their entrance into the bladder and reimplanted more cephalad and lateral to their original position in the trigone, preferably using the Leadbetter-Politano technique to have a wide enough midline area for the new urethral submucosal tunnel. A cross-trigonal reimplant may be used, but the location of the new ureteral submucosal tunnels must be cephalad enough to allow for an adequate length for the new submucosal urethral channel.

Next, a submucosal tunnel is created, 6 cm long × 3 cm wide, beginning at the bladder neck and carried upward and beyond the ureteral orifices. Two stay sutures placed through the bladder musculature on either side of the submucosal tunnel facilitate traction exerted caudally to stretch the tissue. The tunnel must be wide enough to accommodate the bulky neourethra easily (see Fig. 58-1D). An opening is made at the superior aspect of the tunnel. A catheter is now passed caudad to cephalad through the submucosal tunnel. The original stay sutures on the bladder strip are threaded through a straight Keith needle and passed through the flanged end of the catheter. The tubularized strip is drawn into the lumen of the flanged end of the catheter by the two stay sutures. This maneuver is done to ensure that the new tubularized urethra easily slides through the submucosal tunnel without tearing it.

The two stay sutures previously placed at the muscular edges of the submucosal tunnel are used to pull the bladder downward, facilitating passage of the tubularized urethra through the tunnel. Care must be taken to ensure that the entire tubularized urethra is straight and lies within the submucosal tunnel. The two lateral sutures, which were placed at the edges of the tunnel, are now passed through the tissues at the 3- and 9-o'clock positions at the bladder neck and tied. This effectively brings the bladder back down to the bladder neck, and ensures that the new urethra is not unsupported behind the pubic symphysis. The catheter is removed, and the mucosa of the bladder strip is sutured to the bladder mucosa with interrupted stitches (see Fig. 58-1E). The anterior bladder wall is then sutured over the bladder neck at the base of the tubularized strip using interrupted stitches. Attention must be paid to ensure that the tubularized strip is not compressed by the anterior bladder wall, compromising its vascular supply. The ureteral catheters are brought through stab wounds lateral

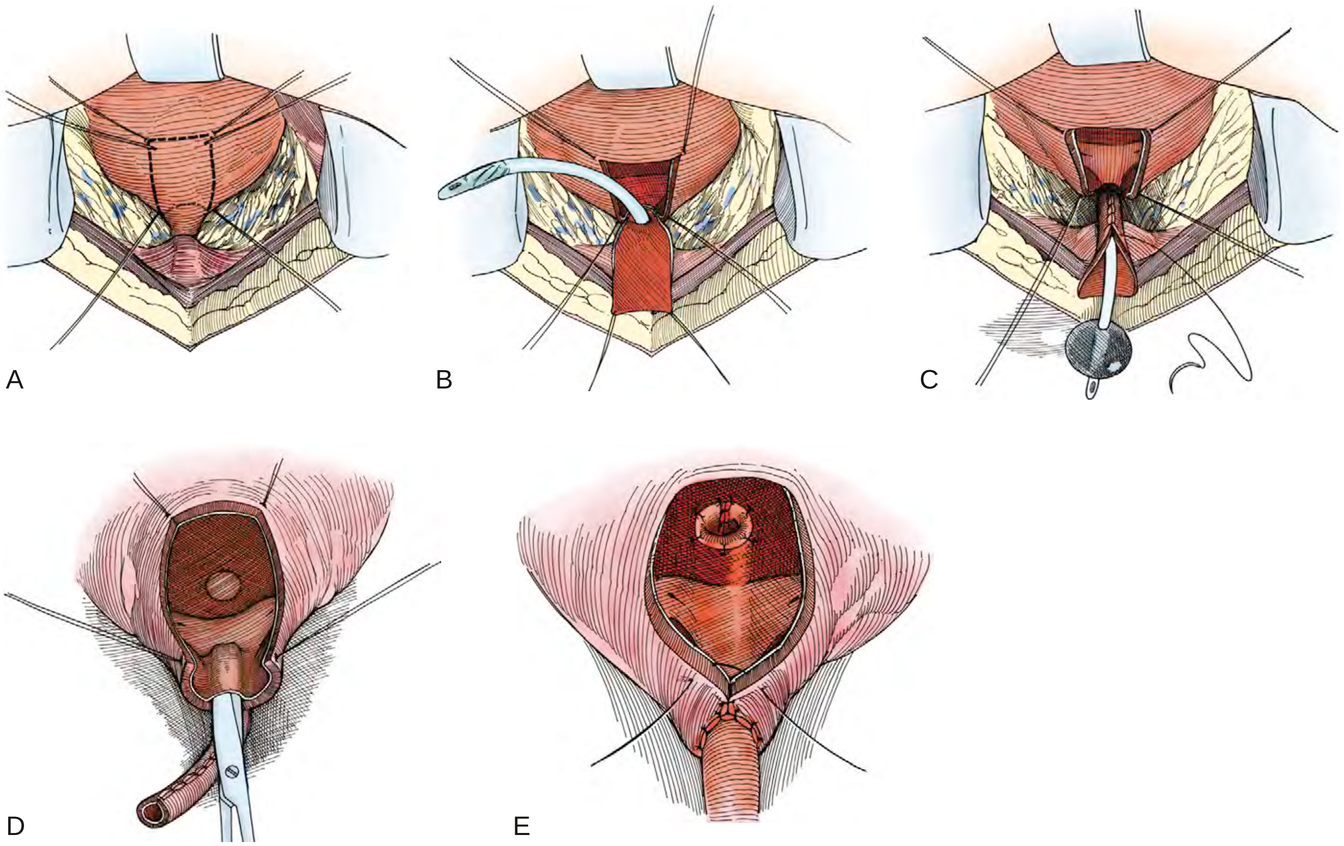

Figure 58-1 Kropp procedure. **A,** Anterior bladder wall flap (5 to 7 cm long × 2 to 2.5 cm wide) is outlined. **B,** The junction of the trigone and the bladder neck is identified from within, and the mucosa of the bladder neck is separated from the urethra. **C,** The anterior bladder flap is tubularized with a one-layer suture (interrupted suture in the last 2 cm). **D,** A posterior trigonal tunnel (6 cm long × 3 cm wide) is created beginning at the bladder neck and carried upward beyond the ureteral orifices. **E,** The tubularized flap is reimplanted in the posterior submucosal tunnel, and the anterior bladder wall is sutured over the bladder neck at the base of the neourethra. (From Hinman F. *Atlas of Pediatric Urologic Surgery.* Philadelphia: Saunders; 1994).

to the bladder, and a suprapubic tube is placed in appropriate position. If augmentation is necessary, the bladder is bivalved by incising it backward in the midline to within 2 cm of the entrance of the neourethra, and the bowel is sutured to the bladder edges.

Results

The Kropp procedure relies on a flap-valve mechanism, and patients achieve dryness because they become retentive. CIC is required for bladder emptying. Although dryness is achieved in 80% of patients,[50] many can experience difficulty with catheterization.[38,51] In 1992, attempting to improve problems related to catheterization after bladder neck reconstructions, De Badiola and associates[52] reported experimental work in dogs in which an anterior bladder mucosal flap was sutured to the posterior bladder wall in an onlay fashion, creating a flap-valve mechanism. Postoperatively, the animals did not have problems with catheterization and showed minimal reduction of bladder capacity.

Similarly attempting to reduce problems with catheterization, Belman and Kaplan[53] suggested another modification to the original Kropp procedure. Instead of complete transection of the bladder neck, only the mucosa is incised transversely to minimize any angulation that might occur when the bladder is totally separated from the urethra. The purpose of this modification was to reduce postoperative catheterization problems, and injury to the posterolateral neurovascular bundles.[53] Next, a submucosal tunnel is made in the midline trigonal area as originally described, and the tubularized anterior bladder flap is reimplanted. Although such modifications made the procedure technically easier and achieved dryness in 95% of patients, significant catheterization problems remained in 44% of the patient population.

More recently, Waters and colleagues[54] described catheterization problems with the Kropp technique. Of 49 patients studied, 72% never experienced difficulty with catheterization after hospital discharge. Difficulty in catheterization developed early in the postoperative period, long after surgery, or intermittently. In most cases, an obvious reason for the difficulty was identified and corrected. In most patients, placement of an indwelling catheter for several weeks solved the problem. They also noted that overdistended bladders were more difficult to catheterize, and recommended more frequent CIC.

Mollard and coworkers[55] reported another modification of the Kropp procedure; these investigators used the technique exclusively in girls with neuropathic bladders. In their opinion, the detrusor flap is often too thick and rigid, and they recommended resection of half or more of the muscle layer, making a thinner and more pliable tube for reimplantation (Fig. 58-2). According to their experience, this resection does not compromise the vascularity, and assists in the creation of the valve mechanism. Dryness was achieved in 13 of 16 girls (81%), who were dry day and night and were easy to catheterize. Bladder augmentation was necessary in 10 of

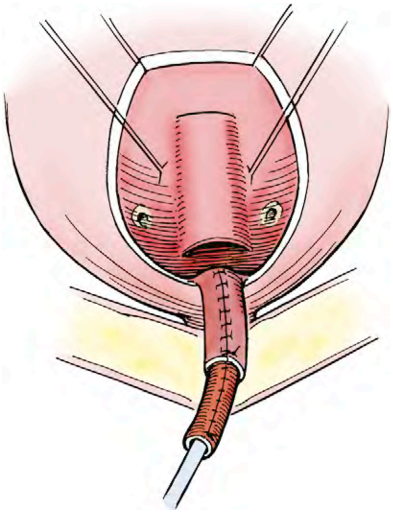

Figure 58-2 Mollard modification of the Kropp procedure. The detrusor of the distal end of the flap is removed, leaving only mucosa and submucosa. This maneuver makes a thinner and more pliable tube for reimplantation into the posterior bladder wall.

16 patients (62%) either simultaneously with the procedure or later. According to these authors this technique is not recommended for boys, in whom neuropathic incontinence is more difficult to treat.

Another attempt to simplify the Kropp procedure, reported by Snodgrass,[56] creates a 6-cm × 2-cm rectangular strip of anterior bladder wall. Similar to the technique of Belman and Kaplan,[53] this method makes no attempt to separate the neck from the remainder of the bladder. The flap is tubularized around an 8F (12F to 14F in adolescents) Foley catheter using absorbable sutures. The mucosa of the bladder is incised longitudinally between the ureteral orifices. The detrusor tube is laid onto this trough, and the distal meatus is secured to the bladder floor musculature. The mucosal edges of the trough are tacked to either side of the tube to bury the suture line completely. No attempt is made to tunnel the detrusor tube submucosally. The anterior bladder wall is closed over the detrusor tube, which is partially extravesical.

Augmentation cystoplasty was performed simultaneously in 20 of 23 patients (86%). Six patients had preoperative vesicoureteral reflux and required simultaneous reimplantation at the bladder neck reconstruction. Dryness of at least 3 hours with surgery plus anticholinergic medications was achieved in 81% of patients. Two additional patients became dry after collagen injection near the meatus of the detrusor tube. Postoperatively, four patients developed significant catheterization problems, and two underwent appendicovesicostomy. New onset of vesicoureteral reflux was noted in nine patients (50%), with spontaneous resolution in five. Although a flap valve is created with this technique, most patients experienced slight leakage when delaying catheterization or omitting anticholinergic therapy. Snodgrass[56] believed that this leakage most likely occurs because approximately one third to one half of the detrusor is extravesical.

Kropp[50] suggests a few important points to avoid difficulty with catheterization: (1) Implant the tube to extend only 2 to 3 cm above the interureteric ridge to avoid kinking when the bladder is full, (2) remove part of the outer musculature in some of the thick detrusors before fashioning the tube, and (3) leave the neourethra with an intraluminal catheter for 4 weeks after surgery.

PIPPI SALLE PROCEDURE

The Pippi Salle procedure is another modification of the Kropp procedure. It creates urethral lengthening using an anterior bladder wall flap, with an intravesical, proximally extended neourethra.[57] This procedure produces a smooth-walled urethra that allows easy catheterization, and a valvelike mechanism similar to the Kropp procedure that compresses and collapses the urethra when the bladder is full. This technique was initially devised to achieve continence in cases of neuropathic incontinence and low urethral resistance,[58] but it has also been used in selected cases of bladder exstrophy and incontinent epispadias when bladder augmentation is anticipated. As with other procedures designed to treat incontinence by producing an intravesical neourethra that acts as a valvelike mechanism, urinary retention is anticipated. The patient must be prepared for lifelong CIC.

Surgical Technique

The patient should be in a hyperextended position whenever this is possible and safe. This position allows better exposure and visualization of the bladder neck. The bladder is exposed, and a wide-based anterior bladder wall flap is outlined. The base of the flap should be 2.5 cm wide, and the dimensions of the flap should narrow progressively to the top, which should be 1.5 cm wide. The flap should be at least 5 cm long (Fig. 58-3A). In the absence of vesicoureteral reflux (the most common scenario), the flap should be prepared with free mucosa extending beyond the distal aspect of the full-thickness flap. This can be facilitated by cutting only the muscular layer of the distal flap and carrying the dissection upward in the submucosal plane, similar to the approach for extravesical ureteral reimplantation. This maneuver results in redundant mucosa hanging in the distal flap; this is used later for its coverage (see Fig. 58-3B).

Additional removal of 0.1 cm of either mucosal edge of the muscular part of the flap is done to avoid overlapping suture lines later during the procedure (see Fig. 58-3C). This excision allows construction of a rectangular mucosal area attached to the flap, which has a larger part of denuded detrusor in its base, the most dangerous place for fistula formation (see Fig. 58-3D).

The ureteral orifices are catheterized and exteriorized laterally in the bladder. Two parallel incisions, 1 cm apart from each other, are made in the posterior trigonal mucosa to expose the muscle (see Fig. 58-3E). The anterior bladder flap is dropped onto the incised posterior trigonal mucosa and sutured in two layers (mucosa-mucosal and muscle-muscular) to the posterior bladder wall in an onlay fashion. An 8F Silastic stent is left in the lumen of the neourethra. The free mucosa at the end of the flap is folded back over the intravesical neourethra, allowing mucosal coverage and facilitating bladder closure (see Fig. 58-3F).

If reimplantation is necessary, both ureters are disconnected before the flap is sutured to the posterior bladder wall and reimplanted in a more cephalad position, using the cross-trigonal method (see Fig. 58-3G). In this case, mucosal coverage of the intravesical urethra is accomplished by dissecting the posterior mucosa lateral to either side of the posterior bladder incisions. After this mobilization, the free mucosa is sutured in the midline, over the intravesical urethra (see Fig. 58-3H). The anterior bladder wall is closed in the midline in a standard fashion, without causing tension on the neourethra. We endeavor to ensure that there is no tension over the neourethra to avoid compression on its base and impairment of its vascular supply. To avoid such tension, it may be necessary to keep part of the neourethra outside the bladder. In our experience, this is often necessary (see Fig. 58-3I). This may be the reason why many patients experience leaking if catheterization is omitted for longer than 5 to 6 hours. This arrangement serves as a welcome "pop-off" mechanism for an overdistended bladder.

If part of the neourethra is left outside the bladder, the extravesical segment can be covered with previously mobilized omentum. Before the bladder closure is ended, an 18F silicone cystostomy tube is inserted and exteriorized by a contralateral stab wound. A schematic lateral view of the neourethra shows its intravesical position (see Fig. 58-3J). If augmentation is necessary, the bladder is opened sagittally in the posterior midline, and the augmented segment is sutured to the edges of the bladder. A laminar silicone drain is left lateral to the bladder. In patients with bladder exstrophy or in incontinent patients with normal bladder innervation, it is advisable to perform a simultaneous appendicovesicostomy. In our experience, although catheters can be easily inserted in the neourethra, these patients may have significant urethral pain and prefer a supravesical route for bladder emptying. The Silastic stent is removed 10 to 14 days after surgery, and

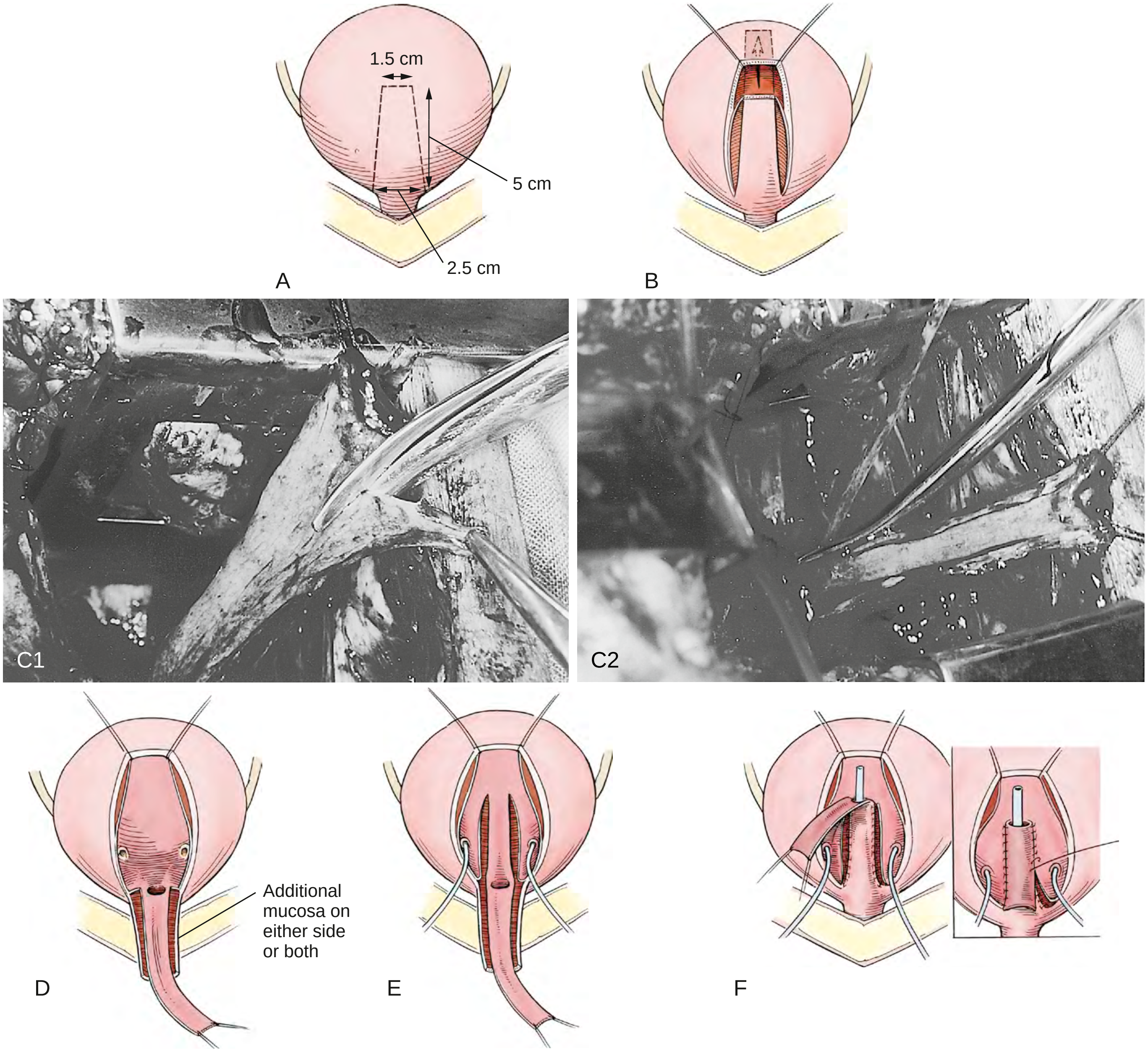

Figure 58-3 Pippi Salle technique. **A,** Anterior bladder wall flap is outlined with a wide base to improve vascular supply. **B,** Only the muscular layer of the distal aspect of the flap is incised. Dissection is carried upward in the submucosal plane to obtain redundant distal mucosa. **C,** Excision of mucosal edges of the flap. **D,** Additional removal of mucosal edge of the muscular part of the flap is done to avoid suture overlapping when it is sutured to the posterior wall. **E,** Two parallel incisions, 1 cm apart, are made in the posterior trigonal mucosa to expose the muscle. **F,** The anterior bladder flap is dropped onto the incised posterior wall and sutured in two layers, in an onlay fashion. The redundant distal mucosa is folded back over the neourethra and sutured to the lateral mucosa.

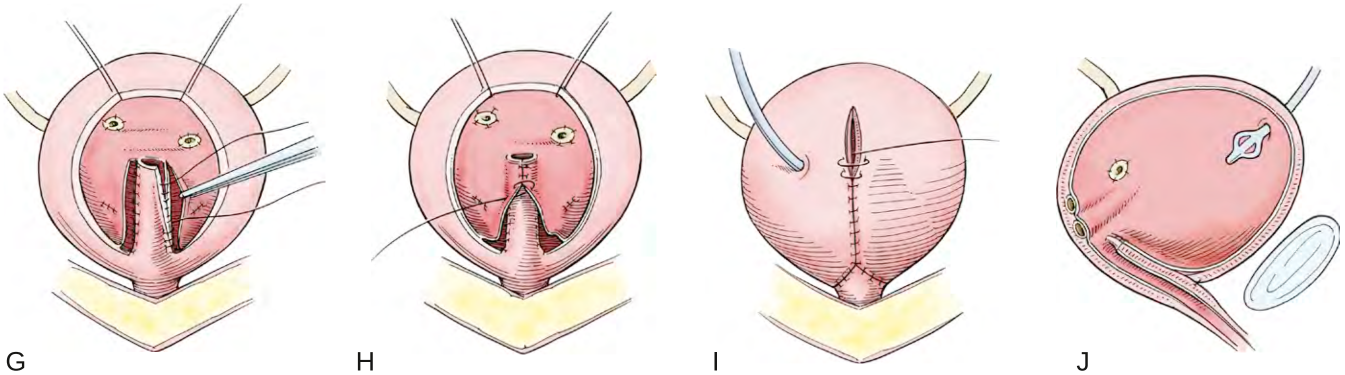

Figure 58-3, cont'd **G,** When reimplantation is necessary, the ureters are reimplanted in a more cephalad position, using the cross-trigonal method. In this case, it is unnecessary to fashion the flap with redundant distal mucosa. **H,** After reimplantation, mucosal coverage of the neourethra is accomplished, dissecting the posterior mucosa lateral to either side of the posterior bladder incisions. **I,** The anterior bladder wall is closed in the midline, causing no tension in the neourethra. If tension is present, it can compromise the vascular supply of the flap leading to ischemia and loss of the flap valve. In most cases, part of the neourethra is kept outside the bladder. **J,** Schematic lateral view of the neourethra. The neourethra is situated inside the bladder and has a flap-valve mechanism. (From Pippi Salle JL. Pippi Salle onlay procedure. *Atlas Urol Clin North Am.* 2001;9:97-107.)

CIC is started. When catheterizations are routinely performed, the cystostomy tube is removed.

In cases of bladder exstrophy or cases with previous bladder operations, a lateralized flap should be fashioned to avoid the midline scar. The flap is sutured to the posterior bladder wall in two layers as described previously.

Results

In a series of patients, most of whom had a neuropathic bladder, Pippi Salle reported dryness for at least 4 hours in 15 of 21 patients (72%),[57,58] and 17 (80%) had acceptable social continence. After his initial experience, Pippi Salle changed the dimensions of the flap to establish a balance between having a narrow enough flap to achieve a good valve mechanism without jeopardizing its vascular supply. This goal was achieved in most patients using a trapezoidal flap shape, removing its mucosal edges. A similar success rate was reported by others.[59-62] Mouriquand and associates[59] reported good results in 72% of patients who achieved dryness, and none experienced problems with catheterization. Similarly, Rink and colleagues[62] reported the use of this technique, and continence was achieved in five of six patients (83%). One of their patients developed a fistula and problems with catheterization. Koyle[60] reported continence in 16 of 17 patients with this technique (94%). Overall, the combined results for this technique achieved a continence rate of 80% (44 of 55 patients); 16% (9 of 55) had problems with catheterization. The success rate with slings is higher in females than males.

SUSPENSION AND PERIURETHRAL SLING PROCEDURES

A suspension or sling procedure is another option for children with a neuropathic bladder. The sling procedure provides external compression and suspension of the bladder neck. One advantage of the sling over the Kropp and Pippi Salle procedures is that with a sling repair, the urethra is sufficiently patent to allow a "pop-off" valve if the intravesical pressure is too high, whereas with the Kropp and Pippi Salle procedures, the reconstructed sphincter is a flap valve that is less likely to leak with high intravesical pressure.

Patient Selection

Children who are candidates for a suspension procedure usually have a neuropathic bladder secondary to myelodysplasia, sacral agenesis, tethered spinal cord, sacrococcygeal teratoma, or a spinal cord tumor. Other situations in which a suspension procedure should be considered include structural injury to the external sphincter, including pelvic fracture; iatrogenic causes (e.g., transurethral incision of the bladder neck in girls); and selected cases of bladder exstrophy or epispadias.

Most children who are candidates for a suspension procedure have been unable to stay dry on CIC despite maximum pharmacologic therapy and optimal frequency of CIC. Generally, children younger than 5 or 6 years have been given insufficient time to assess whether they can stay dry with this form of management. Another aspect regarding patient age is that the bladder neck is much easier to dissect out in prepubertal patients because the bladder is an abdominal organ in that age group. After puberty, in boys, particularly boys who are overweight, isolating the bladder neck can be more challenging.

Children also should have sufficient manual dexterity to be able to perform CIC. Whether a child is ambulatory or uses a wheelchair also is important because children who sit in a wheelchair may have difficulty transferring to a toilet to perform CIC, and often find it easier to empty their bladder through a continent stoma. In such cases, a bladder neck suspension procedure such as a sling often is an effective way of providing sufficient bladder outlet resistance to produce dryness. Before a urethral suspension procedure is performed, the planned method of bladder drainage needs to be determined. It is easier to achieve a continent bladder neck with a fascial sling in girls than in boys, and it is easier to catheterize the female urethra than the male urethra after a fascial sling repair. Consequently, it is appropriate to advise boys that urethral catheterization may be difficult, and that a backup abdominal stoma with the appendix or a Monti-Yang tube might be necessary.

In children with a neuropathic bladder, bladder function is almost always abnormal because they may have detrusor hyperreflexia or poor vesical compliance and an incompetent external sphincter. These children typically are performing regular CIC and taking anticholinergic medications to eliminate detrusor hyperreflexia and α-adrenergic medications to increase bladder neck resistance. When this regimen is ineffective, and incontinence continues, lower urinary tract reconstruction should be considered. In these situations, the relative contributions of the sphincter and the bladder to the child's incontinence need to be determined. The history provides valuable clues to the cause of refractory incontinence, and whether a suspension procedure may be helpful.

Children with a neuropathic bladder and an incompetent sphincter typically have urinary dripping that begins within 1 to 2 hours of catheterization. In contrast, when a child has a dry diaper or underwear for a few hours and then suddenly expels a large volume of urine, the sphincter is likely to be intact, and a bladder problem needs to be addressed. Similarly, if a child has hydronephrosis secondary to vesicoureteral reflux or detrusor-sphincter dyssynergia, the sphincter usually is intact. If it were incompetent, it would be difficult to achieve sufficiently high intravesical pressures to cause upper tract changes. In children who have experienced a pelvic fracture and who have an incompetent sphincter, continuous dribbling usually starts shortly after voiding. In children with exstrophy, the bladder neck is always incompetent at birth, but after bladder closure, particularly with the early total one-stage repair reported by Grady and Mitchell,[63] the sphincter has variable tone. In older children who have undergone the staged closure described by Gearhart and Mathews,[64] the bladder neck is almost always wide after bladder closure. In this case, if the bladder has sufficient capacity, a Young-Dees repair is preferred; however, if the bladder is too small, and augmentation cystoplasty is necessary, a sling might be an option. In addition, in a child with a failed previous bladder neck reconstruction, a periurethral sling should be considered.

The periurethral sling procedure refers to suspension of the proximal urethra and bladder neck to the pubic symphysis or around the rectus muscles with an autologous fascial graft, a cadaveric allograft, or a prosthetic material. In women with stress urinary incontinence secondary to intrinsic sphincter deficiency, this procedure has provided the best long-term results,[65] and is considered the "gold standard." In planning the sling, a decision should be made preoperatively about whether the patient will be catheterizing his or her urethra or if the bladder will be drained through a continent stoma. This decision is important because the sling may be made tighter if the patient will be catheterizing an abdominal stoma.

Surgical Technique

The sling is placed around the bladder neck. The plane around the bladder neck is identical to that for placement of an AUS. In girls, there are three approaches: retropubic, retrovesical, and transvaginal. In boys, there are two approaches: retropubic and retrovesical.

Approach to the Bladder Neck

In patients undergoing a sling repair, proper bladder neck exposure is a key component to success. Because most of these patients undergo augmentation enterocystoplasty with or without a Mitrofanoff appendicovesicostomy, a midline incision that extends 1 to 2 cm superior to the umbilicus is usually used. A transverse incision in the lower abdomen with transection of the rectus fascia and musculature also may be appropriate. A catheter is left in the bladder to aid in identification of the urethra. These patients should be kept in a latex-free operating environment.

In the retropubic approach, the inferior aspect of the bladder is mobilized, and the bladder neck is defined. This approach is easiest in prepubertal and thin patients. It is slightly more difficult in adolescents and adults because the bladder is a pelvic rather than an abdominal organ in these age groups. In obese patients, it can be particularly difficult. If augmentation cystoplasty is planned, the bladder should be opened before beginning the dissection. This maneuver makes it easier to identify the correct plane around the bladder neck. In contrast, if augmentation cystoplasty is not performed, whether to open the bladder is left to the surgeon's discretion.

The tissue plane adjacent to the bladder neck on each side is dissected using a right-angle dissector (Fig. 58-4A). The puboprostatic ligaments sometimes are incised. Adolescents and adults often have large veins adjacent to the bladder neck. A urethral catheter helps identify the bladder neck. The right-angle clamp is passed behind the bladder neck. Particular care should be taken not to injure either the muscle fibers of the bladder neck anteriorly or the vagina or rectum posteriorly. When the plane has been achieved behind the bladder neck, umbilical tape is passed through the plane. A Penrose drain should not be used because latex precautions are being observed. An alternative to using umbilical tape is to use the middle finger of a nonlatex glove or a Jackson-Pratt drain. Anterior traction is placed on the umbilical tape, and by careful blunt dissection a 2.5-cm-wide plane is established. Attention to hemostasis is important. The surgeon should ascertain that no bladder neck injury has occurred. The umbilical tape is left in place until the end of the reconstructive procedure, when the sling material is placed.

In the retrovesical technique described by Lottmann and colleagues,[66] it makes no difference whether the bladder is opened. With the bladder partially full, the peritoneal attachment to the dome of the bladder is identified and is separated off the detrusor. The bladder is then emptied. The plane behind the bladder is developed by sharp and blunt dissection inferiorly to the bladder neck (see Fig. 58-4B-E). In girls, the vagina is easily identified, and in boys, the plane anterior to the seminal vesicles is identified. The plane of dissection is medial to insertion of the ureters. When the bladder neck is reached, the right-angle clamp can be passed laterally on each side through the soft tissues to the space adjacent to the bladder neck. Umbilical tape is passed from the left side through the retrovesical space and then advanced on to the right side of the bladder neck. Next, the plane of dissection around the bladder neck is developed as described in the previous paragraph. This dissection seems to be the safest method for avoiding injury to the bladder neck, vagina, and rectum in patients who have not undergone previous bladder neck surgery. Whether it causes denervation of the bladder is uncertain, however. This consideration is not important if the patient will be emptying the bladder by CIC.

In women, a transvaginal approach is appropriate. A U-shaped incision is made in the anterior vaginal wall. Traction sutures are placed on the vaginal flap, and the flap is mobilized by sharp dissection. The bladder neck is easily identified, and insertion of a urethral catheter aids in identifying the sides of the bladder neck. A right-angle clamp is passed anteriorly on either side of the bladder neck, and umbilical tape is brought around the bladder neck as previously described.

Choice of Sling Material

In most cases, the sling is taken from the rectus fascia as a free graft. The rectus fascia usually is easily obtained through a suprapubic incision. The only potential disadvantage of rectus fascia is that if the patient is obese, abdominal wall closure may be difficult. In such cases, two options are available. The first option is to use rectus fascia and close the abdominal wall using a polypropylene or Marlex mesh. Another option is to use fascia lata from the thigh rather than rectus fascia for the graft.[67] The disadvantage of this approach is that most urologists are unfamiliar with the surgical anatomy of the thigh, and it may be necessary to ask another surgeon to harvest the fascia lata graft.

A synthetic material that has shown efficacy is small intestinal submucosa (SIS), which is available as 1-ply or 4-ply, which is stronger.[68] The material may be folded onto itself to improve graft strength. The long-term efficacy of SIS has been favorable. Other synthetic materials, such as monofilament polypropylene (Marlex, CR Bard, Covington, RI) and synthetic polymer implant (ProteGen, Boston Scientific Corp., Natick, MA), have been associated with urethral erosion.[69,70]

In addition to autologous fascia, use of allograft fascia has generated some interest.[71] There has been extensive experience using cadaveric fascia lata, mostly for nonurologic applications. In a large series in which Wright and colleagues[72] compared allograft fascia lata with autologous rectus fascia, the mean operative time and hospital stay were significantly shorter when using allograft. The disadvantage of the allograft is that it is more expensive.

One other operative point is that the graft may be sandwiched inside polyglycolic acid mesh. Strong (single 0)

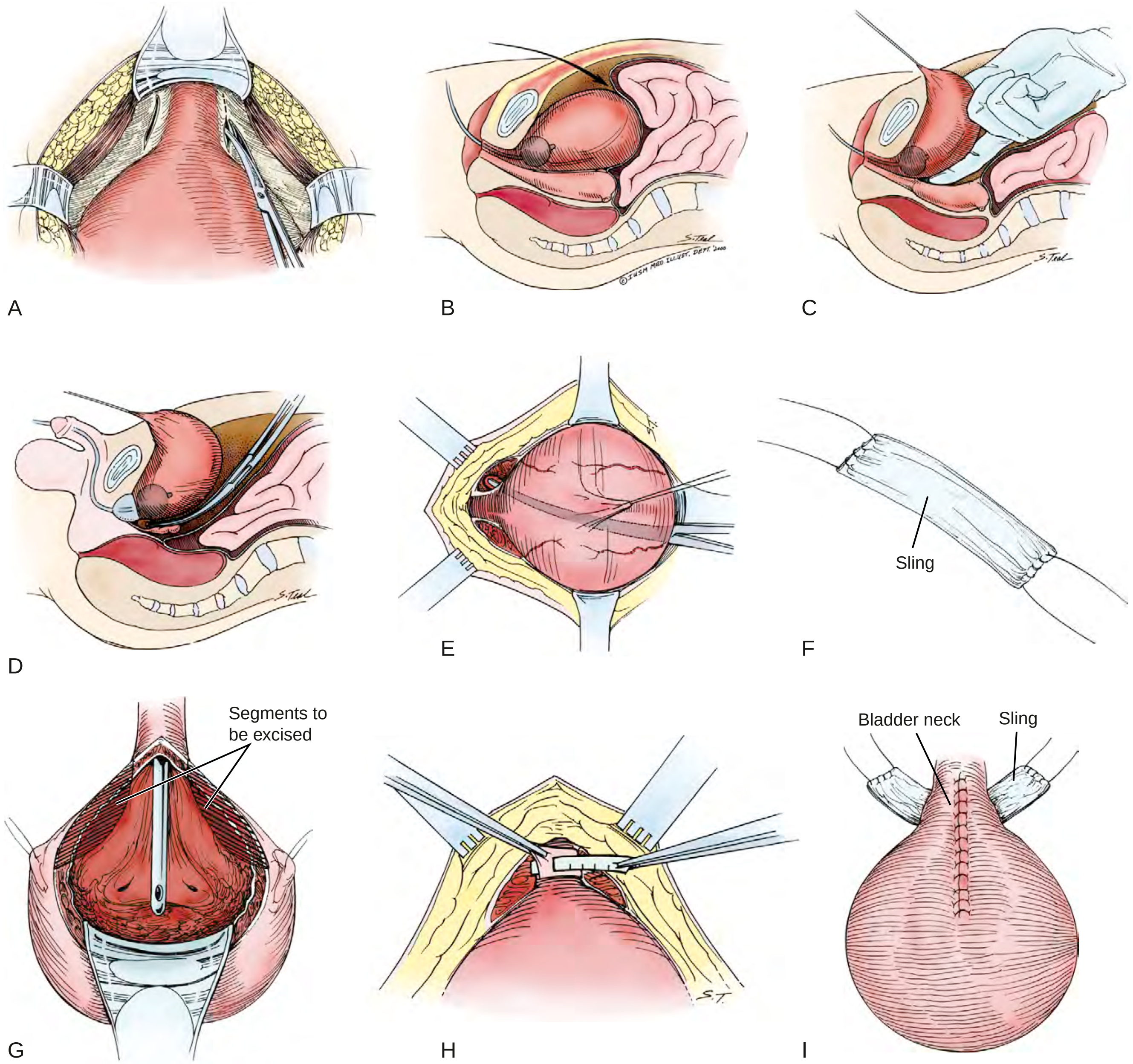

Figure 58-4 Technique for periurethral sling procedure. **A,** Incision is made along the endopelvic fascia on either side of the urethra. **B** and **C,** Lottmann technique for developing retrovesical plane in girls. **D** and **E,** Lottmann technique for developing retrovesical plane in boys. **F,** The graft is fixed on each end with a running baseball stitch using polypropylene suture. **G,** The bladder neck is tapered by excising part of the detrusor muscle on each side adjacent to the bladder neck. **H,** Distance around tapered bladder neck is measured. **I,** The sling is placed behind the bladder neck. (**B-E,** From Lottmann H, Traxer O, Aigrain Y, et al. La voie d'abord retro-vesicale pour l'implantation du sphincter artificiel AMS 800 chez l'enfant et l'adolescent: technique et resultants chez huit patients. *Ann Urol (Paris).* 1999;33:357.)

polypropylene sutures should be placed along each end of the graft. In the past, a U-stitch was placed, but a running "baseball" stitch along each end seems to provide excellent strength (see Fig. 58-4F).

Sling Placement

Placement of the periurethral sling generally is done at the end of the reconstructive procedure because the tension on the sling can be adjusted, and one can test the strength of the sling after the bladder is closed. There are several general techniques for sling placement. As originally described, the sling was placed around the urethra and suspended up against the pubic symphysis in a "U" shape (Fig. 58-5A and B). This technique provided 270-degree urethral compression and has generally been effective in female patients; however, it has not been as reliable in male patients. More recently, some workers have advocated crisscrossing the sling to provide 360-degree urethral compression (see Fig. 58-5C). The crisscrossing can cause variable circumferential compression, however, and the urethra can sometimes be difficult to catheterize.

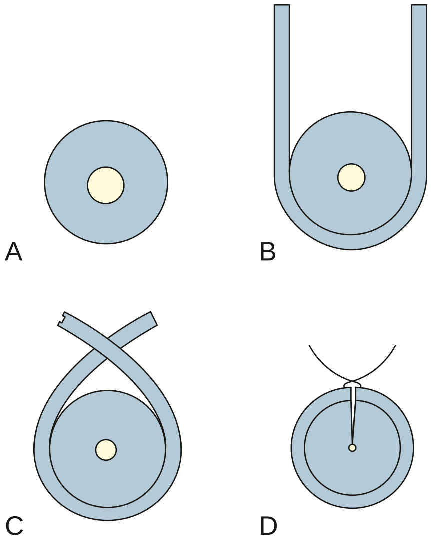

Figure 58-5 Various methods of sling placement. **A,** Incompetent urethra. **B,** U-shaped position of a periurethral sling. The ends are tied to the pubic symphysis or rectus fascia, or are brought together anterior to the rectus fascia. This method provides 270-degree compression. **C,** Technique of crisscrossing ends of the sling, providing 360-degree compression. **D,** Bladder neck is narrowed, and the fascial graft is shortened such that the ends of the graft barely meet anterior to bladder neck. The graft should be fixed to the bladder neck in two places. The sutures on each end of the graft are crisscrossed to provide 360-degree bladder neck compression, and the sutures are tied anterior to the rectus fascia.

In our opinion, the most effective method for sling placement takes advantage of the bladder neck–tapering techniques described by Herschorn and Radomski[73] and by Walker and colleagues[74] in conjunction with circumferential sling placement (see Fig. 58-5D). With the bladder open, the bladder neck is mobilized using the Lottmann technique. A vertical cystotomy is made through the anterior bladder neck. With a urethral catheter in place, the bladder neck and proximal urethra are narrowed to 14F to 18F in adolescents and adults and to 10F to 12F in prepubertal patients.

Bladder neck tapering is achieved by excising a wedge from each side of the bladder neck and proximal urethra (see Fig 58-4G). The urethral edges are reapproximated with interrupted 2-0 polyglycolic acid sutures. Next, the distance around the bladder neck is measured with umbilical tape (see Fig 58-4H). The fascial or SIS graft is obtained. The width of the graft should be approximately 2 cm, and the graft length should be 3 to 5 mm less than the urethral circumference. When traction is placed on each end of the sling, the graft has a tendency to curl or roll up. Consequently, fixation of the graft to the bladder neck in two to three places with 4-0 polyglycolic acid sutures is helpful (see Fig. 58-4I).

The suture ends are crisscrossed anterior to the urethra, providing 360-degree urethral compression by the graft (Fig. 58-6A). A free needle is placed on each of the four suture ends, and they are advanced through the abdominal fascia lateral to the rectus muscle. The two suture ends from each side are tied together anterior to the rectus fascia with a surgeon's knot. Tension may be adjusted to provide optimal urethral compression. The tension necessary for urethral closure can be tested by manually compressing the bladder to observe for urethral

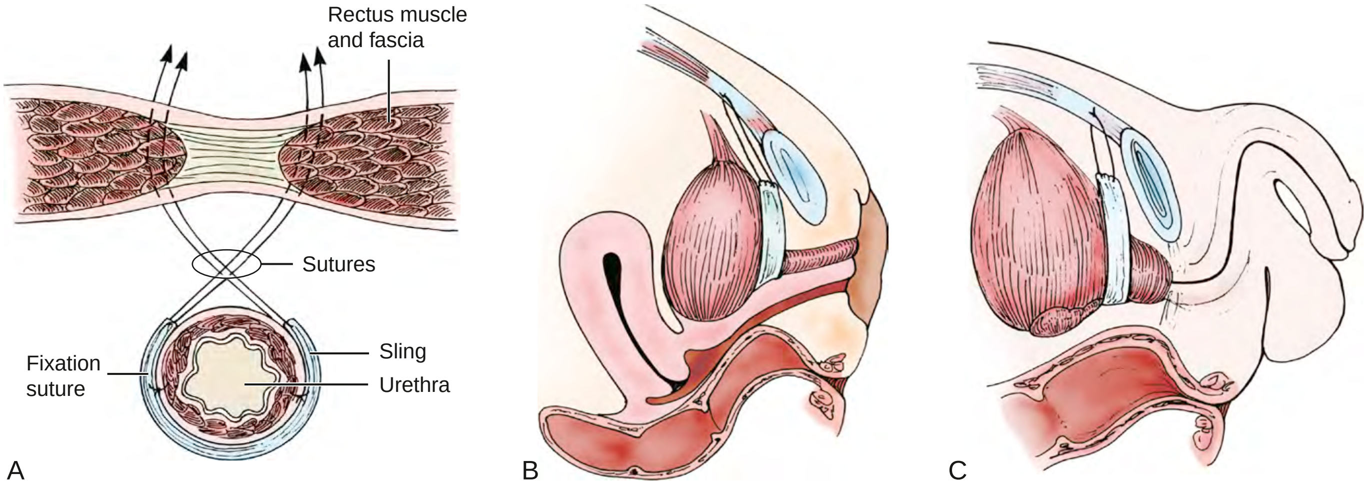

Figure 58-6 Placement of the periurethral sling. **A,** The sutures on each end of the graft are crisscrossed anterior to the bladder neck, brought through the rectus fascia on each side, and tied anterior to the rectus fascia, providing 360-degree urethral compression. **B,** Placement of sling in girls. **C,** Placement of sling in boys.

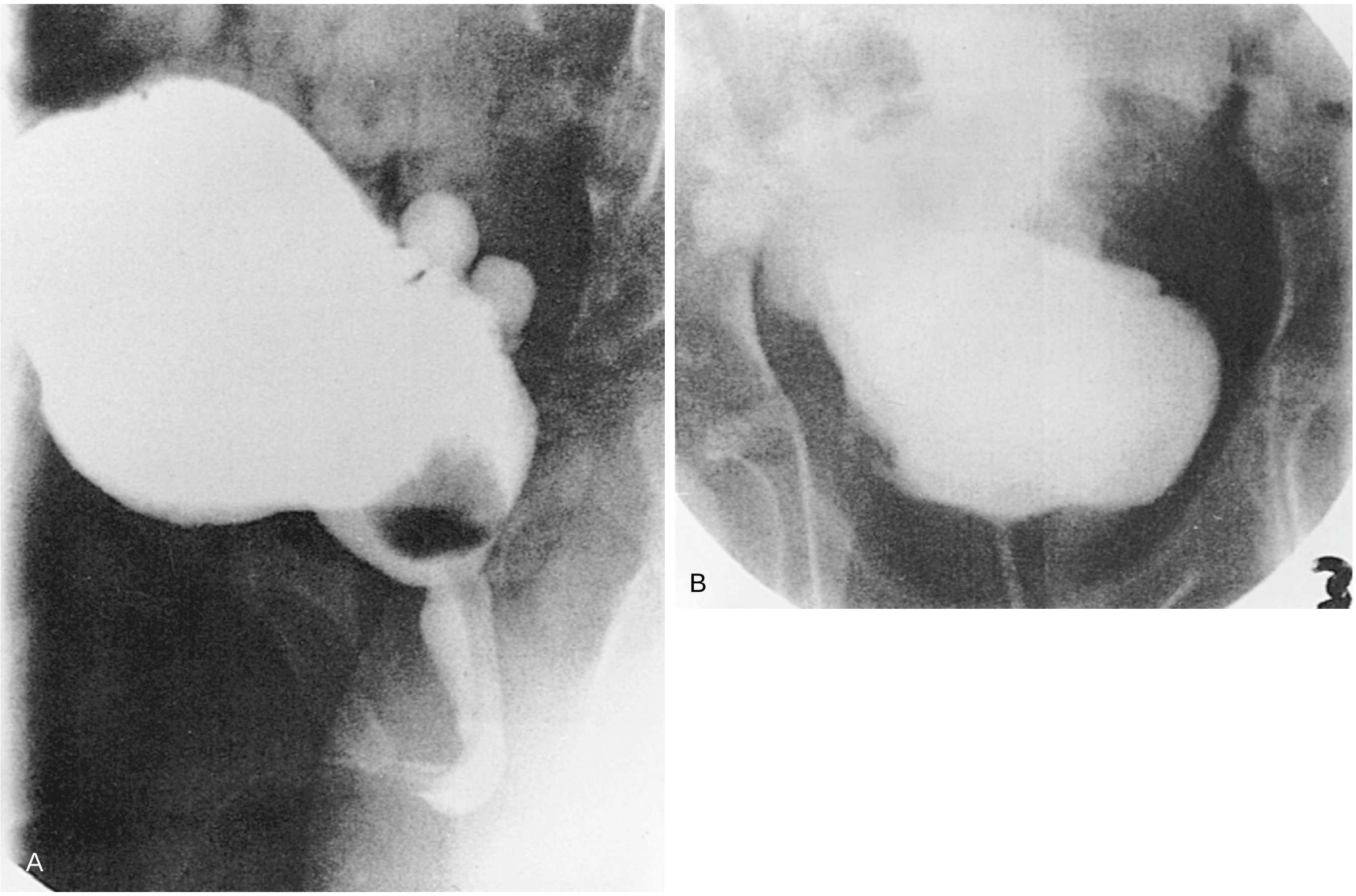

Figure 58-7 A 10-year-old boy with myelodysplasia. **A,** Preoperative cystogram shows incompetent bladder neck and small trabeculated bladder. The patient underwent enterocystoplasty and periurethral sling. **B,** Postoperative cystogram shows elevation of bladder neck. (From Elder JS. Periurethral and puboprostatic sling repair for incontinence in patients with myelodysplasia. *J Urol.* 1990;144:434.)

leakage. As the sling tension is increased, the surgeon should ascertain that urethral catheterization can be accomplished. It is necessary to place much more tension around the male urethra than the female urethra to achieve continence (see Fig. 58-6B and C).

Many patients with a neuropathic bladder undergoing sling placement ambulate in a wheelchair. These individuals often prefer a Mitrofanoff catheterizable abdominal stoma to urethral catheterization. In such cases, the sling tension may be increased slightly to maximize the likelihood of having a continent reconstructed sphincter.

Postoperatively, whether to leave an indwelling urethral catheter is optional; if so, an 8F pediatric feeding tube seems optimal. A suprapubic catheter is left indwelling for 2 to 3 weeks before catheterization is initiated. This catheter should be latex-free, and either a Silastic balloon catheter or a Jackson-Pratt drain may be left in the bladder for continuous urinary drainage. At 2 to 3 weeks postoperatively, urethral catheterization with a coudé catheter is recommended if the patient is to perform urethral CIC (Fig. 58-7).

The success rate of the sling has varied among many different centers and techniques, but is comparable or superior to all of the other techniques that have been described for the surgical management of insufficient outlet resistance (Table 58-1).[75] Postoperatively, patients should undergo regular upper tract imaging with a renal ultrasound scan or noncontrast CT scan. In addition, regular urine cultures and, if enterocystoplasty has been performed, serum electrolyte determinations should be performed.

Complications of Periurethral Sling

The most common complication after a sling procedure is incontinence, which may result from inadequate outlet resistance from the sling, detrusor hyperreflexia, inadequate bladder drainage during catheterization, infrequent catheterization, infection, erosion of the urethra by the sling, or loss of the fascial graft. The urine should be sterilized, and the pattern of incontinence should be clarified. If the sling tension is inadequate, urinary leakage tends to be continuous despite effective bladder drainage. If the sling repair was performed without enterocystoplasty, the most likely causes of incontinence are a small-capacity bladder, detrusor hyperreflexia, or both. Even if the bladder was areflexic preoperatively, the bladder dynamics may change after an increase in outlet resistance, and hyperreflexia that is unresponsive to anticholinergic therapy may occur.

Complete re-evaluation including cystography, upper tract imaging, and urodynamic studies should be performed. Cystoscopy may be necessary to determine whether the sling has eroded. If the sling tension is too loose, transurethral injection with dextranomer/hyaluronic acid (Deflux) may be beneficial, but a secondary sling repair or implantation of an AUS may be necessary.[28] If hyperreflexia

Table 58-1 Results of Sling Urethropexy in Children with Neuropathic Bladder

		Patients				Dry		
Series	**Age (yr)**	**Male**	**Female**	**Total**	**Technique**	**Male**	**Female**	**Total**
McGuire et al[76]	Not reported	0	8	8	Transvaginal		8/8	8/8
Raz et al[77]	Not reported	0	3	3	Transvaginal		3/3	3/3
Raz et al[78]	10-22 (mean 16)	4	0	4	Periurethral	4/4		4/4
Bauer et al[79]	6-22 (mean 14)	0	11	11	Periurethral		8/11	8/11
Elder[80]	7-25 (mean 13)	4	10	14	Periurethral	3/4	9/10	12/14
Herschorn and Radomski[73]	17-40 (mean 27)	13	0	13	Periurethral; bladder neck tapering	9/11*		9/11*
Decter[81]	5-26 (mean 11)	4	6	10	Periurethral; rectus or iliotibial fascia	3/6	2/4	5/10
Gormley et al[82]	10-19	0	15	15	Transvaginal		11/13	11/13
Kakizaki et al[83]	3-72	10	3	13	Periurethral; rectus or fascia lata			9/13
Walker et al[45]	4-23 (mean 12)	8	9	17	Rectus fascial wrap; bladder neck tapering	8/8	9*/9*	17/17
Kurzrock et al[84]	7-23	15	9	24	Bladder wall pedicle wraparound sling	10/15	9*/9*	19/24
Perez et al[85]	4-17 (mean 9)	15	24	39	Periurethral sling; some with crisscross	9/13	13*/23*	22/36
Barthold et al[86]	Not reported	7	20	27	Rectus fascial sling			5/10
					Rectus sling wrap			5/13
Austin et al[87]	8-18 (mean 14)	8	10	18	Rectus fascial sling	7/8	7/10	14/18
Nguyen et al[88]	7-19 (median 13)	7	0	7	Rectus fascial sling	1/7		1/7
Dik et al[89]	1-17 (mean 9)	0	24	24	Transvaginal		19/24	19/24
Castellan et al[90]	4-40 (mean 11)	15	43	58	Rectus fascial sling	13/15	38/43	51/58
Misseri et al[91]	3-10 (mean 9)	15	21	36	SIS sling	10/15	17/21	27/36
Snodgrass et al[92]	3-17 (mean 8.6)	18	12	30	Rectus fascial sling; none augmented	13/18	12/12	25/30

*Does not include two patients with erosion secondary to use of Marlex mesh.
SIS, small intestinal submucosa.

is significant and does not respond to anticholinergic therapy, either augmentation cystoplasty or detrusor myotomy (autoaugmentation) is necessary. It is important to be certain that the sphincter tightness is sufficient, however. If urethral erosion is caused by the sling, a secondary sling repair and artificial sphincter implantation usually are unsuccessful, and bladder neck ligation and creation of a continent stoma are often necessary.

Another complication of the sling is difficulty with urethral catheterization. This problem may occur if there is significant urethral angulation, if the bladder neck was narrowed too much, if the sling tension is too tight, or if the urethral mucosa was circumferentially disrupted during the dissection, resulting in a urethral stricture. If there is significant angulation, use of a coudé or hydrophilic catheter often solves the problem. Angulation may result if the sling was crisscrossed, however, and in this situation a revision of the sling probably is necessary. Another option in the presence of difficult catheterization is to create a continent stoma.

A rare complication is distal ureteral obstruction if the sling was placed too close to the insertion of one or both ureters. It may be possible to correct this problem by either retrograde or antegrade dilation, but in most cases ureteroneocystostomy is necessary.

BLADDER NECK SUSPENSION ALONE

Bladder neck suspension procedures have been used in the past for the management of an incompetent sphincter in girls with a neuropathic bladder. These techniques are not applicable in boys. Raz and colleagues[77] performed a Burch bladder neck suspension in conjunction with enterocystoplasty in 42 girls and women, and 79% became dry. Freedman and associates[93] described 26 female patients who underwent either a colposuspension or Marshall-Marchetti-Krantz procedure and enterocystoplasty, and 88% were subsequently dry during the day. Although these results are encouraging, success with bladder neck suspension procedures in women with stress incontinence has not been as durable as with sling repairs, and for this reason the periurethral sling is preferred.

BLADDER NECK CLOSURE

In children with intractable urinary incontinence despite previous attempts at bladder neck/sphincter reconstruction, bladder neck closure can be performed as the final surgical procedure to achieve dryness in conjunction with continent urinary diversion and with or without concomitant enterocystoplasty. The patient and the family must understand that the procedure cannot be reversed.

The bladder is opened in the midline. The incision extends from the dome of the bladder inferiorly to a point 1 to 2 cm from the bladder neck. The bladder neck is mobilized from the sides and proceeds posteriorly. The bladder neck is transected, and the posterior bladder wall is mobilized away from the vagina in girls and away from the rectum in boys. This posterior wall is rolled anteriorly and incorporated into the ultimate bladder closure. Whether to tie off the distal urethra is up to the discretion of the surgeon. The bladder should be drained postoperatively for 2 to 3 weeks to ensure that the bladder has healed.

The most common complication of bladder neck closure is a distal urethral fistula. In a compilation of three more recent series of this procedure involving 40 patients, 4 (10%) developed a fistula.[94-96] The potential for this complication may be minimized by developing an inferior-based rectus muscle flap.

MALE SLING

A newer form of anti-incontinence therapy that shows promise in boys is the bone-anchored suburethral sling. The polypropylene male perineal sling system (InVance, American Medical Systems, Minnetonka, MN) has been used successfully in adult males with post-prostatectomy incontinence. This procedure has demonstrated low morbidity and reliable improvement of post-prostatectomy incontinence in this patient population.[97]

Patients are positioned in an exaggerated lithotomy position. A 3-cm incision is made in the midline of the perineum at a point just below the scrotum. The superficial tissue is left intact over the bulbospongiosus. Lateral dissection is performed, exposing the medial and superior aspects of the bilateral descending pubic rami. Titanium bone screws (5.5 mm length by 3.2 mm diameter) preloaded with two 1-0 polypropylene sutures are then placed in each descending pubic ramus. The most proximal screws are placed at the confluence of the inferior pubic ramus and the pubis. Care is taken to avoid placement of the screws in the arcuate ligament. The subsequent screws are placed sequentially approximately 5 mm apart. The polypropylene mesh to be implemented as the sling is then measured and cut to an oval configuration approximately 2 by 4 cm. The mesh is then secured to the bone screws. Sling tension can be adjusted to provide maximal urethral compression while still permitting passage of the patient's standard urethral catheter. This level of compression is significantly higher than that described for post-prostatectomy incontinence, in which urinary retention is a complication rather than the goal of the procedure. The recent use of an antibiotic-impregnated mesh may reduce the risk of infection.

In the initial report, 6 adolescent boys with neuropathic bladder secondary to myelodysplasia underwent placement of the male sling as an outpatient.[98] All 6 patients reported immediate and complete continence and no patient reported inability to catheterize by way of the urethra. Two subsequently developed local infection and underwent mesh removal, one of which was eventually replaced. Overall, 5 of 6 have remained continent with follow-up as long as 39 months. These results are quite preliminary and have only been reported in adolescents. However, this form of treatment is much less invasive than the periurethral sling and eventually it could become a preferred form of anti-incontinence surgery.

REFERENCES

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CHAPTER 59

ARTIFICIAL URINARY SPHINCTER

Ricardo González and Lisandro Piaggio

The treatment of urinary incontinence by means of prostheses that compress the urethra and replace the function of the sphincter dates back to the early part of the 20th century with the Cunningham clamp, which provided external compression of the penile urethra in incontinent men. In the 1940s, Foley[1] published and patented a device that provided intermittent compression of the surgically isolated penile urethra by means of an inflatable cuff. Three decades later, Bradley, a neurologist with a strong interest in bladder dysfunction; Timm, a bioengineer; and Scott, a urologist,[2] developed an implantable device that they called an *artificial genitourinary sphincter.* The use of this device (AS 721), which had separate opening and closing pumps and relied on a low-pressure valve to prevent overfilling of the cuff, was first reported in 1973.[3] The problems of tissue erosion and frequent mechanical malfunction led to changes in design and technical refinements that resulted in the device currently used, the AS800, which was introduced in 1983.[4,5]

Since the 1980s, three other prostheses have become available. One, the Rosen prosthesis, had very poor results and has been discontinued.[6] An attempt to produce a less expensive device for use in countries with fewer resources was described in 1997, but the experience that has been published is limited, and the failure rate with 23 months of mean follow-up is very high (40%).[7] A more recently described new device has not been used in children.[8] This chapter deals only with the mechanisms, technique of implantation, results, follow-up, and complications of the AMS 800 prosthesis (American Medical Systems, Minnetonka, MN).

AMS 800

The AMS 800 artificial urinary sphincter (AUS) consists of an inflatable cuff that can be implanted around the bladder neck or bulbous urethra, a pressure-regulating balloon that transmits a predetermined pressure to the cuff and maintains it closed (inflated), and a unit containing a pump and valve mechanism that allows the deflation of the cuff and its reinflation. This pump is implanted into the scrotum or labium (Figs. 59-1, 59-2, and 59-3). The cuffs are available in sizes ranging from 4 to 11 cm in circumference, and the balloon pressure ranges from 50 to 80 cm H_2O at 10-cm H_2O increments. At rest, the pressure in the balloon is at equilibrium with the pressure in the cuff, maintaining the urethra compressed at the predetermined pressure. By squeezing the pump, the fluid is transferred from the cuff to the balloon, opening the urethra and permitting voiding or catheterization. The cuff refills slowly and spontaneously through a system of valves and fluid resistors located in the pump unit (Fig. 59-4).

In the pump and control unit, there is a button that interrupts the flow of fluid from the balloon to the cuff so that the cuff may be left empty (open) or "deactivated." This is useful during the early postoperative period when delayed activation is desired to allow tissue healing and resolution of the scrotal or labial edema and tenderness. Vigorous squeezing of the pump re-establishes fluid flow (activation), and the cuff refills (see arrow in Fig. 59-1). Leaving the cuff open or deactivated is also necessary when an indwelling urethral catheter is required. The current prosthesis owes its increased success compared with the previous models to a lubricated narrow back cuff design that prolongs its life, and the pressure-regulating balloon that has made tissue erosion owing to pressure rare.[8]

INDICATIONS, PATIENT EVALUATION, AND PATIENT SELECTION

The AUS is used to treat incontinence resulting from sphincteric incompetence. Most pediatric patients in whom the AUS is implanted have neurogenic bladder and sphincter dysfunction. There is also experience with the use of the AUS in epispadias, bladder exstrophy, urethral trauma, and posterior urethral valves.

As with any other procedure designed to increase outlet resistance to enhance continence, it is important to determine that sphincteric incompetence is a factor in the patient's incontinence. It is also necessary to evaluate the potential of the bladder to store sufficient volumes of urine at low pressure after urethral resistance is established. This is not always easy because most patients with long-standing incontinence have reduced bladder capacity. In addition, in patients in whom the AUS is most commonly implanted—patients with neurogenic dysfunction—the cause of incontinence often includes a component of decreased bladder capacity and compliance.[9] In these patients, cystometrography is best performed with bladder occlusion, but this technique is sometimes difficult to perform in children.[10]

The diagnosis of sphincteric incompetence is clear in a neurogenic patient with good capacity and compliance who leaks between catheterizations. When the compliance and capacity are diminished, the use of videourodynamics or fluoroscopic cystography with the patient in the upright position gives information regarding the ability of the bladder neck to close. The external sphincter is best evaluated by needle electromyography. We rely less on the leak point pressure and find the abdominal leak pressure unreliable in pediatric patients.[11]

If the bladder capacity and compliance are diminished, the bladder neck is open, and the external sphincter is denervated, bladder augmentation alone would not render the patient continent. A bladder outlet enhancement procedure must be done in conjunction with the augmentation to ensure continence.[12]

The evaluation of the outlet tends to be more straightforward in patients with normally innervated bladders, such as patients with epispadias, exstrophy, and trauma. The evaluation should include a baseline study of the upper tracts comprising renal ultrasonography, voiding cystourethrography, and, when indicated, renal scintigraphy. Reflux, if present, is best corrected surgically or endoscopically before the contemplated AUS implantation. When low-grade reflux is present, and an augmentation is contemplated, resolution may occur after the operation.

The patient or caregivers must accept and be able to perform intermittent catheterization. Even patients who

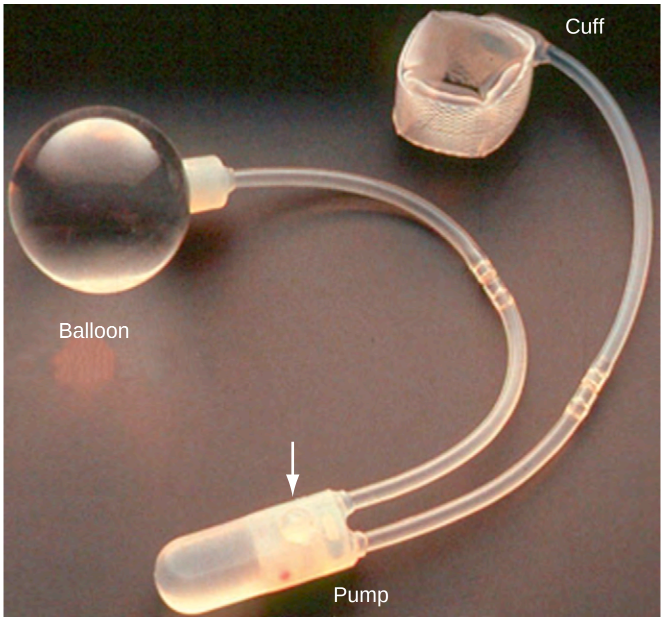

Figure 59-1 AMS 800 artificial urinary sphincter. The *arrow* indicates the deactivation button.

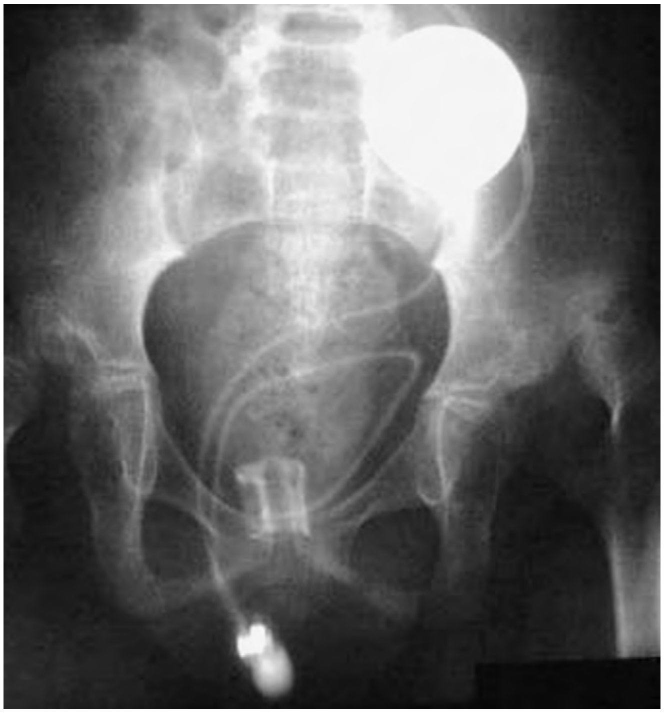

Figure 59-2 Plain radiograph showing the components of the AMS 800 artificial urinary sphincter filled with contrast medium.

void spontaneously must be able to perform catheterization because transient or permanent retention can occur after the implantation. Evaluation of the social situation, family support, cognitive ability, and manual dexterity is also essential to success. Despite contrary opinions, a lack of ambulation is not a strict contraindication to implantation.

Fecal continence must be addressed at the time of considering surgery for urinary incontinence. Achievement of urinary continence without fecal continence is futile. In small children, fecal continence usually can be achieved with a regimen of enemas to provide complete, periodic evacuation of the colon. In older children and adolescents, the construction of a continent cecostomy to provide access for antegrade enemas is useful to increase self-reliance.[13]

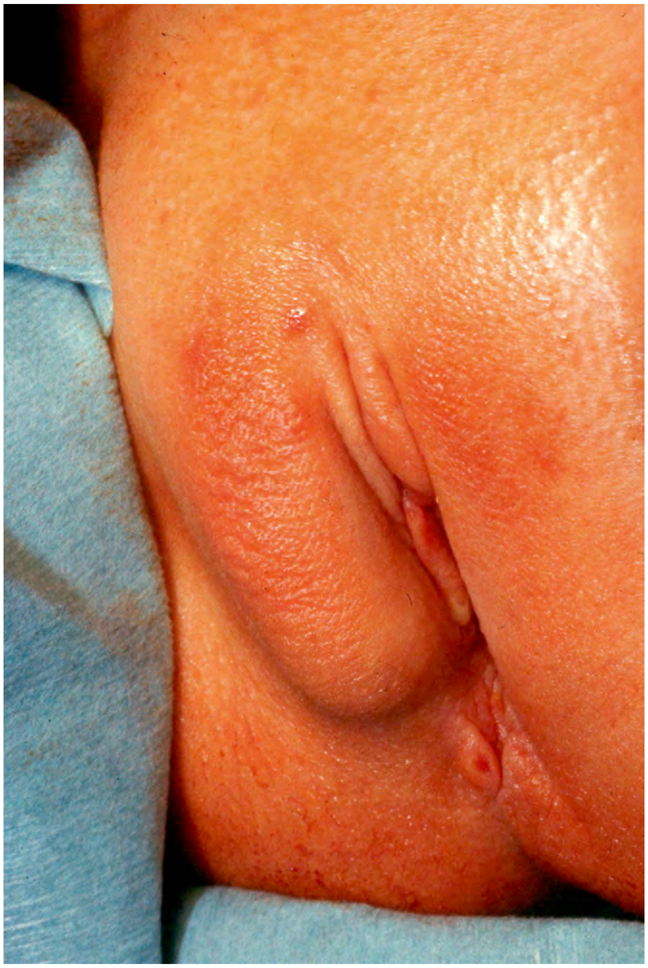

Figure 59-3 Prepubertal girl with pump of an AMS 800 implanted in the labium major.

The aim of AUS implantation is mainly to increase outlet resistance, not to achieve spontaneous voiding. Realistic expectations by surgeons and families are important for postoperative satisfaction. The age of implantation does not alter the long-term outcome. We believe that congenital incontinence should be treated early, and that children, whenever possible, should be out of diapers by the time they are in first grade.[13,14]

PREOPERATIVE PREPARATION

The preparation of the patient is important to minimize complications. Infection of the AUS is a catastrophic event that requires the removal of the device and usually rules out the possibility of a future implant at the same site. Most AUS infections can be attributed to surgical contamination during implantation. Every effort to prevent infections is necessary even if there are no strong data to support all of the following recommendations.

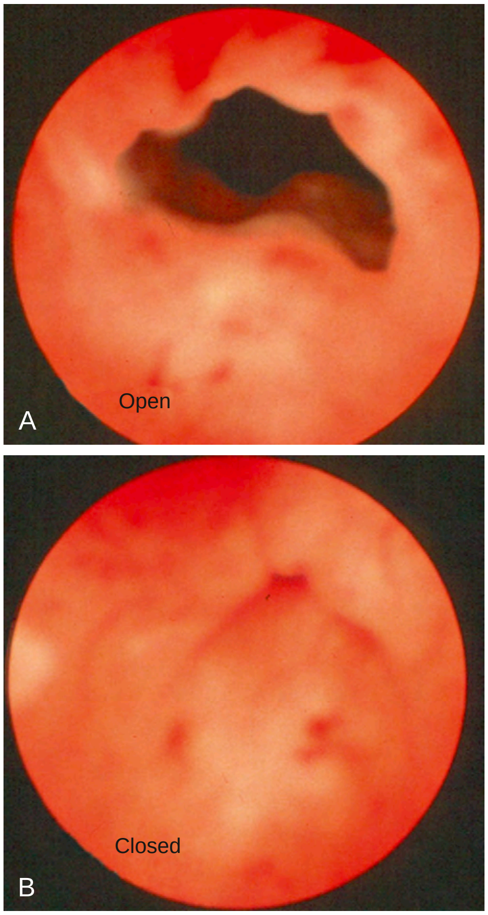

Figure 59-4 Endoscopic views of a male bladder neck with the artificial sphincter open **(A)** and closed **(B).**

The patient undergoes a mechanical bowel preparation, and broad-spectrum antibiotic therapy is started before the operation to cover bowel and skin flora and urine culture according to sensitivities. There should be no septic foci of infection in the skin, such as decubitus ulcers. The urine should be sterile. Urine culture is obtained with time enough to start a treatment 1 week before surgery. Because the urine of patients with a prior bladder augmentation is difficult to sterilize, we start repeated bladder irrigations with antibiotics at the time of admission.

SURGICAL TECHNIQUE

The bladder is partially filled with an antibiotic solution, and the catheter is removed. Boys are positioned supine on the table, and the genitalia are included in the surgical field. Girls are positioned flat with the legs spread apart. The vulva and vagina are prepared with povidone-iodine solution. Impermeable drapes are secured to create a watertight field. Operating team turnovers should be minimized. It is important that the scrub nurse and circulating nurse are familiar with the procedure, and that a strict sterile technique is followed to avoid infections.

The incision is most commonly a low transverse abdominal incision. Flaps of skin and subcutaneous tissue are elevated, allowing access to the fascia for a midline incision from the umbilicus to the pubis. A midline skin incision can also be used. A catheter is placed in the bladder, and the bladder is emptied before the dissection of the retropubic space is begun. The retropubic space is entered by blunt dissection, and the veins of the Santorini plexus that lay on the anterior surface of the seminal vesicles or vagina are identified. They are an important landmark to find the plane around the bladder neck. Using the balloon of the Foley catheter to define the bladder neck might be misleading and should be avoided. The veins that are in the way of the dissection are divided between ligatures.

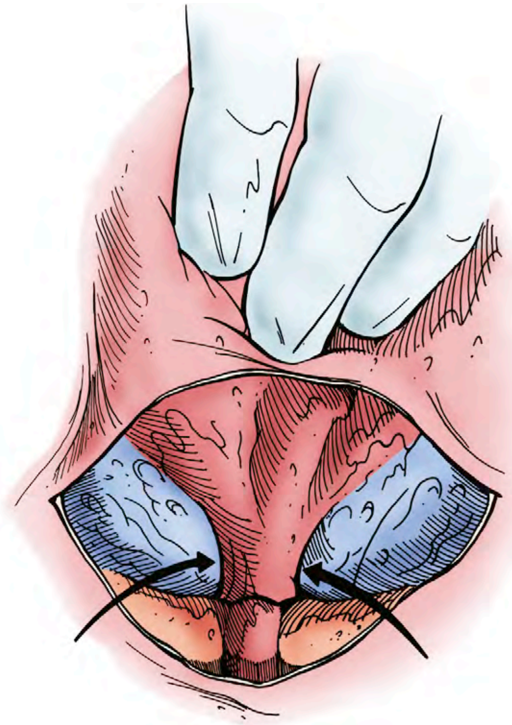

Figure 59-5 Schematic representation of initial exposure of the anterior aspect of the bladder neck shows the veins of the Santorini plexus on both sides *(arrows)*.

Cephalad retraction of the bladder is helpful at this point (Fig. 59-5). In girls, a finger is placed in the vagina, and the bladder neck is dissected posteriorly bluntly with a dissector against the anterior vaginal wall. In boys, the dissection is also blunt. Frequent palpation allows identification of the posterior bladder neck and the vasa (Fig. 59-6). The plane of dissection should be between the vasa and the bladder. The temptation to pass a right-angle clamp blindly to expedite the dissection must be resisted to avoid injuries of the bladder neck or related structures. In boys, the dissection is easier before puberty.

When the dissection is completed, a vessel loop is placed around the bladder neck. The bladder is filled with a dilute methylene blue solution to check for leaks. If a leak is encountered (<10% of cases), an anterior cystotomy is made, staying away from the bladder neck. The inadvertent perforation is closed from within the bladder in two layers, and the test is repeated. If continued leakage is observed, the AUS should not be implanted.

The circumference of the bladder neck is measured, and the preprimed but empty cuff is implanted. The cuff should fit snugly around the bladder neck, but should be able to be rotated. A slightly looser cuff is used if the patient is expected to void spontaneously.

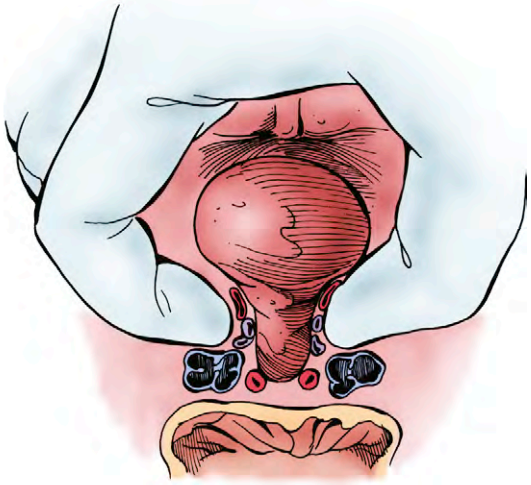

Figure 59-6 Schematic representation of structures palpated during the dissection of the bladder neck in a male patient. The catheter and its balloon should not be used as the sole landmarks.

A preperitoneal space is created on the left side of the abdomen, and the chosen balloon primed with 22 to 23 mL of fluid is placed. The tubes from the balloon and the cuff are brought to the subcutaneous space, and the fascia is closed. A space is bluntly created in the right hemiscrotum (in front of the testis) or in the labium major, and the appropriate connections are made. We prefer to make the connections with the Quick Connectors (American Medical Systems, Minnetonka, MN) provided in the kit. Before the connections are made, air is purged from the tubing with priming solution, and contamination with body fluids is avoided. Only two connections are necessary, between the two tubes from the pump to the tube cuff and the tube of the balloon. The tubes are color-coded to avoid errors. The system is tested and left in a deactivated mode with the cuff empty and the pump full. We prefer to leave the connection in the subcutaneous space for easy access and identification in case of reoperation. The fascia, subcutaneous tissue, and skin are closed. A compressive dressing is applied to avoid seromas. Drains are avoided. Antibiotic irrigation is used throughout the procedure.

The priming of the system should be done with care to avoid contamination of the priming solution with body fluids because proteinaceous material may block the fluid resistor. Air must be purged out of the system during priming. Because the silicone membrane is semipermeable, the priming solution must be iso-osmotic with the extracellular fluid to avoid volume changes. Normal saline solution is acceptable, but limits the imaging possibilities during follow-up. Dilute contrast material is preferred except for patients with a history of contrast agent allergy. To allow normal function of the device, only fluids mixed according to the instructions provided by the manufacturer should be used.[15]

The sphincter is left deactivated in the open position for 6 weeks. In a simple implantation, the catheter is removed after 24 or 48 hours, and intermittent catheterization is begun. This is usually necessary even in patients who eventually void spontaneously.

When a bladder augmentation is done simultaneously with AUS implantation, we proceed as follows. The prevesical space and the dissection around the bladder neck are carried out before the peritoneum is opened. A loop is left around the bladder neck. The peritoneum is opened, and the enterocystoplasty is performed. When possible, we prefer the seromuscular colocystoplasty with preservation of the urothelium without a suprapubic cystostomy.[12,16,17] When the cystoplasty is completed, the surgical field is thoroughly irrigated, gloves are changed, and the AUS is implanted.

RESULTS

Most pediatric patients in whom the AUS is implanted have neurogenic incontinence. In this section, we analyze separately the results according to the cause of incontinence.

Neurogenic Incontinence

In children and young adults with neurogenic incontinence, AUS results from several centers have been published. It is convenient to consider separately continence, the possibility of spontaneous voiding versus the need for intermittent catheterization, and the need for bladder augmentation.

Continence can be achieved in 54% to 100% of patients. The continence rate of patients followed for 5 to 10 years with the AMS 800 is about 85% (Table 59-1). When all patients in whom the AUS was successfully implanted are considered, that is, excluding patients in whom the prosthesis was removed because of infection or erosion, the expected continence rate is higher.[18] To minimize complications, we prefer not to open the bladder at the time of a simple implantation of the AUS. If open antireflux surgery is needed, it is done a few months before the implantation. Injection therapy can be carried out under the same anesthesia. As described later, when needed, we combine AUS implantation and enterocystoplasty and even construction of a continent stoma, but one must be extremely diligent in the preparation of the patient and in the surgical technique.[17]

Spontaneous voiding in this patient population can be expected in 10% to 47%, predominantly in patients with spontaneous voiding preoperatively (see Table 59-1).[19] Some boys who void spontaneously before puberty become dependent on intermittent catheterization after puberty. Replacing the cuff for one of a larger circumference has not restored voiding in these patients.[20] The safety of combining intermittent catheterization with the AUS is well documented.[21] Some authors continue the practice of sphincterotomy before AUS implantation to facilitate spontaneous voiding, but in view of the wide acceptance of intermittent catheterization, we seldom do it.

The decision to augment the bladder before or at the time of sphincter implantation is not always clear-cut. Although universal augmentation may protect the upper tracts, its potential complications, including metabolic acidosis, the possibility of stunted growth, and the risk of bladder perforation and peritonitis, persuade us to continue to be selective in its performance.[22] We do not perform augmentation in patients who have compliant, atonic bladders with a capacity of at least 60% of that expected for age.[23] Other authors have reported, however, that preoperative urodynamic studies failed to predict the subsequent need for augmentation in a similar population.[24] The compatibility of augmentation and AUS implantation is well documented.[17,25] Meticulous preoperative preparation and surgical technique is essential for success. When a selective policy of bladder augmentation is adhered to, and patients are followed carefully, augmentation is needed in 9% to 65% of cases depending on patient selection and the surgeon's attitude (Table 59-2).[19,26,27]

Non-neurogenic Incontinence

We favor the use of the AUS to treat incontinence associated with epispadias. A patient with untreated epispadias is an ideal candidate for AUS implantation because the bladder

Table 59-1 Continence Rate in Major Reported Series

Reference	No. Patients/No. Neurogenic Bladder	Spontaneous Voiding (%)	Continence Rate Overall/with Functioning AUS (%)	Mean Follow-up (yr)
Kryger et al[19]	32/28	26	56/95	15.4
Levesque et al[47]	2 groups: 36/32; 18/17	36	59/82; 83/100	10;5
González et al[48]	19/19	27	84/84	8
Hafez et al[18]	79/74	43	80/90	12.5
Castera et al[35]	49/38	47	67/85 (bladder neck cuff)	7.5
Singh and Thomas[49]	90/90	22	92	4
Simeoni et al[50]	107/107		76/87	5
Herndon et al[51]	134/107	22	68/92	7.5
Barrett et al[52]	59/46		80/85	3.5
Lopez-Pereira et al[27]	35/35	10	91/100	5.5

AUS, artificial urinary sphincter.

Table 59-2 Rate of Augmentation, Loss of Bladder Compliance, and Renal Damage in Major Series

Reference	No. Patients/ No. Neurogenic Bladder	Loss of Compliance Requiring Augmentation (%)	Overall Augmentation Rate (%)	Postoperative Hydronephrosis (%)	Postoperative Reflux (%)	Postoperative Renal Insufficiency (%)
Kryger et al[19]	32/28	37	47	21	5	
Levesque et al[47]	2 groups: 36/32; 18/17	37				15
González et al[48]	19/19	27	37	11	5	0
Hafez et al[18]	79/74	5	12	10		
Castera et al[35]	49/38	5	27	4		
Singh and Thomas[49]	90/90		0			
Simeoni et al[50]	107/107	25	41	1	6	
Herndon et al[51]	134/107	28			7	
Barrett et al[52]	59/46	5	5	5	5	
Lopez-Pereira et al[27]	35/35	31	57			

neck is virgin, and bladder sensation and contractility are normal. The bladder may be reduced in capacity, but often expands with time and anticholinergic therapy. Spontaneous voiding is common (González R, unpublished observations, 2000).

The situation is different in patients with bladder exstrophy after a failed bladder neck reconstruction. In these cases, the erosion rate is higher.[18,28] Because most patients with failed exstrophy require a bladder augmentation and a continent catheterizable stoma, solutions other than the AUS may be appropriate to increase bladder outlet resistance. Nevertheless, other authors have proposed the use of the AUS after failed bladder neck reconstruction as an alternative to a repeat reconstruction or a continent diversion in selected patients.[29] More recently, Ruiz and colleagues[30] reported excellent continence rates in patients with bladder exstrophy, epispadias, and anorectal malformations.

There are other rare situations in which the AUS is useful in young patients. With AUS placement, we have successfully treated incontinence secondary to urethral trauma in girls, persistent postpubertal incontinence in boys with posterior urethral valves, and iatrogenic incontinence.[31] These cases are uncommon, however, and there are no reports of large series with long-term follow-up. In contrast, Ashley and Husmann[32] reported a high rate of failures in boys with a history of urethral disruption.

COMPLICATIONS

The potential complications of AUS implantation are infection, erosion, AUS malfunction, and changes in bladder compliance with subsequent recurrence of incontinence or the new development of hydronephrosis.

Infection

The infection rate for a newly implanted AUS should be less than 5%. Preventive measures are discussed in the section of preoperative preparation. We normally perform a preoperative bowel preparation even if an augmentation is not

Table 59-3 **Complications and Survival of Artificial Urinary Sphincter in Major Reported Series**

Reference	AUS Model	Functioning AUS at Last Follow-up (%)	Mean Follow-up (yr)	Revisions per Patient per Year	Mean Time to Failure (yr)	Previous Bladder Neck Surgery (%)	Erosions (%)	Infections (%)	Mean Survival of AUS (%)
Kryger et al[19]	AS 792, 742, 800	58	15.4	0.08 (0.03 after 1987)	4.8	34	25	15	70
Levesque et al[47]	AS 792, 742, 800	78	10, 5	0.1		13	6	0	72
González et al[48]			8	0.2			0	0	
Hafez et al[18]	AS 792, 742, 800	75	12.5	0.35			20		80
Castera et al[35]	AS 800	80	7.5		3	16	20	2	65 (85 without previous bladder neck surgery)
Singh and Thomas[49]	AS 792, 800		4				7.8	6.7	
Simeoni et al[50]	AS 800	87	5		4.6	28	17	7	
Herndon et al[51]	AS 792, 742, 800	76	7.5	0.085		22	14	3	62
Barrett et al[52]	AS 800	93	3.5			27	2	3	
Lopez-Pereira et al[27]	AS800	91	5.5				9		91
Ruiz et al[30]	AS 800	86	6.5						86

AUS, artificial urinary sphincter.

contemplated. During the operation, the wound is repeatedly irrigated with antibiotics. With all these measures, if an infection occurs, it is usually not acute but chronic, with mild but persistent or recurrent inflammatory signs and symptoms. Infections predispose to tissue erosion at the site of the pump or, more rarely, at the bladder neck. If infection is suspected, cystoscopy to assess the bladder neck status should be performed. The treatment consists of removal of the prosthesis. If no bladder neck erosion has occurred, reimplantation can be attempted many months or years later (Table 59-3).

Erosions

With older AUS models, erosions secondary to pressure necrosis were common.[33,34] With the AMS 800 with a narrow back cuff[5] implanted around a bladder not previously operated, erosions are rare. In the report by Castera and coworkers[35] of 49 children with a mean follow-up of 7.2 years, the mean time to erosion was 2 years (1 month to 9 years). Castera and coworkers[35] attributed the 20% rate of erosions in their series to infection, previous bladder neck surgery, or fibrosis after pelvic trauma. In the Toronto experience with 89 patients and a mean follow-up of 12.5 years, 20% of the AUS were removed because of erosion after a mean of 5.6 years.[18] Bladder neck erosions manifest with signs of infection or recurrent incontinence, but they may be silent for a long time, particularly in patients without bacteriuria who void spontaneously. Scrotal or labial erosions are usually the result of infection or pressure in wheelchair-bound patients. Previous bladder neck surgery predisposes to erosion.[28]

The treatment is AUS removal. A bladder neck erosion precludes future successful implantation in the same location. Delayed activation of the sphincter, initially advocated to reduce the erosion risk, is now routinely performed with new implants (see Table 59-3).[36]

Malfunction

Mechanical malfunction of the device leads to recurrent incontinence or, more rarely, an inability to void. Inadvertent deactivation of the AUS by the patient in the open or closed position can lead to incontinence or urinary retention. Physical examination establishes the diagnosis, and patient education prevents its recurrence.

Similar to all mechanical devices, the AUS has a finite life span. Among the technologic advances that made the AUS an acceptable therapeutic modality, the increase in the revision-free interval has been as important as the decrease in the risk of erosions. For sphincters implanted since 1987, 80% are expected to function 10 years later without revision.[18,19] The most common cause for AUS replacement is a loss of fluid because of breaks in the silicone membrane of the cuff. Others have reported shorter half-life and discourage this method of treatment, an opinion that based on our experience we do not share (see Table 59-3).[37] The fluid loss is usually gradual and may not be obvious on the initial examination. Whenever possible, we fill the system with dilute contrast medium and obtain an early radiograph of the pelvis as a baseline for future comparisons.[38] We find this method more reliable than ultrasound measurements (Fig. 59-7). Other causes of malfunction are tubing kinks and component malfunction (see Table 59-3).[18]

Changes in Bladder Compliance

It is well known that changes in bladder compliance can occur when bladder outlet resistance is increased, particularly in patients with neurogenic bladder dysfunction.[39] The change in compliance may be apparent only after AUS implantation, however, and may have preceded the implantation, given the difficulty in performing and interpreting cystometrograms in patients with very low outlet resistance even when bladder neck occlusion is attempted during the study.[10] In other instances, the changes may be due to the neurologic changes often seen in myelomeningocele patients secondary to a tethered spinal cord.

Periodic urodynamic reassessment should be part of the routine follow-up of patients with the AUS who have not had bladder augmentation. Prompt intervention to decrease intravesical pressure with anticholinergics, the institution of intermittent catheterization, and, when needed, bladder augmentation should minimize the risk of new reflux, upper tract dilation, and renal failure. The reported risk of renal failure varies from 2% to 15%.[12,24,40] The worst cases are in patients not compliant with the prescribed regimen of intermittent catheterization or follow-up evaluations. This underscores the importance of proper patient selection, taking into account the family situation, access to medical care, and understanding of the risks.

Changes in bladder compliance can be expected to occur in 20% to 40% of patients without augmentation after AUS implantation. Overall augmentation rate in combination with AUS implantation has been reported to be 12% to 65% (see Table 59-2). When a bladder augmentation is needed at the time of implantation or subsequently, our preferred approach is to use the seromuscular colocystoplasty technique, provided that a catheterizable stoma is not mandatory. In a retrospective analysis of 27 patients, we achieved an 89% continence rate at about 2 years.[12]

Postoperative Vesicoureteral Reflux

Changes in bladder compliance often lead to the development of new reflux, which is a common factor in the development of renal damage. Reflux after AUS implantation warrants prompt evaluation and treatment. If bladder capacity or compliance is diminished, anticholinergic medications are administered. If there is no response to the pharmacologic treatment, bladder augmentation with or without antireflux surgery should be performed either at the time of augmentation or later, if reflux persists. If possible, endoscopic treatment of the reflux is preferred to reimplantation. High-grade reflux, particularly if long-standing, seldom resolves without an antireflux procedure (see Table 59-2).

Persistent or Recurrent Incontinence

When incontinence persists or recurs after AUS implantation, a systematic evaluation is needed to elucidate its cause. It is important that this evaluation be done promptly after the onset of incontinence because it may be an indication of increased intravesical pressure and impending renal damage. The physical examination determines whether the device is cycling properly. In the early stages of a slow fluid loss, the sphincter may appear to cycle normally on examination, however. Accidental deactivation and severe loss of fluid from the system are evident on examination. In these cases, the pump is either collapsed or full. If the pump is full, it suffices to squeeze it to reactivate the system. If the pump is collapsed, the control unit located above the pump is gently twisted to deflate the unidirectional valves and to allow refilling of the pump and reactivation.

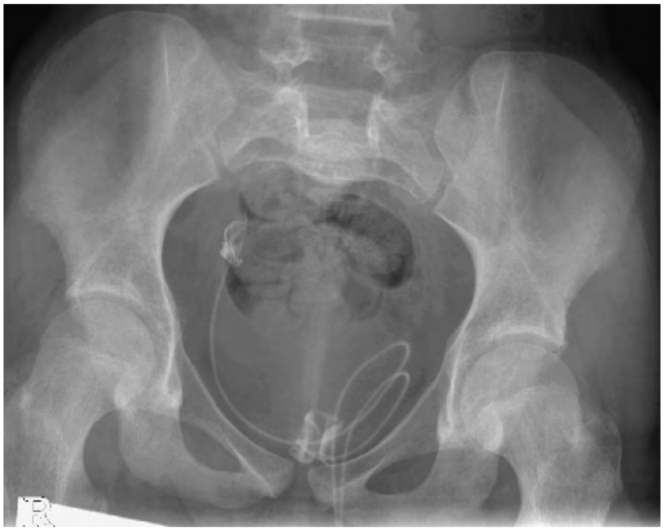

Figure 59-7 Plain radiograph showing loss of contrast medium in the components of an AMS 800 artificial urinary sphincter in a patient with recurrent incontinence.

Overflow incontinence must be ruled out not only in patients who void spontaneously, but also in patients who perform intermittent catheterization because they may not empty the bladder completely. Urinalysis and culturing are important because cystitis can produce temporary reversible bladder instability. Next, a plain radiograph of the pelvis allows comparison of the balloon size with previous images to detect fluid loss (see Fig. 59-6). The presence of gas within the system indicates a leak. Cystoscopy is necessary to rule out erosion of the bladder neck, and should always be performed before AUS replacement.

A cystometrogram is important in detecting changes in bladder compliance. If altered compliance is detected, cystography and renal ultrasonography are needed to rule out reflux and hydronephrosis. Finally, poor coaptation of the bladder neck by too large a cuff is a diagnosis of exclusion. This may rarely be the result of a technical error, but most often is the consequence of atrophy of the tissues surrounded by the cuff. The solution is replacement. Kinkless tubing and good surgical technique have largely eliminated AUS malfunction resulting from kinked tubes.

The treatment for each cause of recurrent or persistent incontinence is usually self-evident. When replacing the AUS for loss of fluid, we replace all the components. Techniques described to locate the point of the leak are cumbersome and unreliable. It is to the patient's advantage to have a completely new device implanted.

Trauma occasionally can cause breaks in the tubes. During the operation to correct the problem, it is important to recognize that blood-containing or protein-containing fluids may have gained access to the system, and the system should be thoroughly flushed with dilute contrast medium or completely replaced. Other authors prefer to replace only the suspected defective component, something that we do only exceptionally.[41,42]

More recently, we have observed two patients who became incontinent after botulinum type A toxin injection to treat decreased bladder compliance. In both patients, the balloon had been punctured during the injection. Because botulinum toxin injection is at best a temporary treatment for increased intravesical pressure, in patients with an AUS we continue to recommend a seromuscular or conventional colocystoplasty.[43]

FOLLOW-UP

All patients with the conditions that lead to implantation of an AUS require lifelong follow-up regardless of the treatment they have received. Follow-up is particularly important after AUS implantation because it is such an effective method to increase bladder outlet resistance that changes in bladder and kidney function may ensue. Shortly after implantation, renal ultrasonography is necessary to rule out hydronephrosis secondary to compression or entrapment of the ureters by the cuff. Mild, transient dilation is sometimes observed. In the first year after implantation, we perform cystometrography every 3 months to detect possible changes in bladder function, particularly changes arising from preoperative misdiagnosis. Thereafter, patients are followed with yearly examinations, renal and bladder ultrasound scans, and cystometrography. Any changes in continence or voiding habits are promptly evaluated.

ALTERNATIVE TECHNIQUES

Although the technique described here has worked well for us for many years, some authors have found dissection of the bladder neck intimidating. Castro Díaz prefers to open the bladder electively to facilitate bladder neck dissection (Castro Díaz D, personal communication). In 1999, Lottmann and coworkers[44] described an extraperitoneal, retrovesical approach to facilitate the dissection.

It is beyond the scope of this chapter to discuss surgical alternatives to increase outlet resistance. Suffice it to say that we consider the AUS the treatment of choice for boys and girls with urinary sphincter incompetence who void spontaneously. Boys dependent on intermittent catheterization are also best treated with the AUS because alternative methods yield inferior results. Girls dependent on intermittent catheterization might benefit equally from aponeurotic slings or the AUS.[45,46] Long-term data on results of slings are lacking. We almost never perform bladder neck tubularization procedures except as alternatives to bladder neck closure. The need to reimplant the ureters and augment the bladder and difficult catheterization through the tubularized bladder neck are the principal disadvantages of these procedures.[26]

CONCLUSION

Since 1975, the AUS has evolved into a reliable and effective means of treating sphincteric incompetence in children and young adults. Meticulous attention to detail during patient selection, implantation, and follow-up are crucial to the success of treatment.

REFERENCES

For complete list of references log onto www.expertconsult.com

CHAPTER 60

INJECTABLE BULKING AGENTS IN THE TREATMENT OF PEDIATRIC URINARY INCONTINENCE

Julian Wan, David Bloom, and John Park

Urinary continence is a fundamental component of normal life. Toilet training is a happy milestone of development that mothers tend to recall with great accuracy and detail in terms of age and circumstance. Later in life, the maintenance of continence along with mobility, and sound vision and hearing are regarded as the cardinal signs of a happy independent old age. The causes of incontinence in children are numerous; incontinence is a symptom and not a specific disease or condition. At one end of the spectrum of incontinence is simple nocturnal enuresis resulting from delayed nocturnal antidiuresis or failure of arousal by a full bladder. At the other end of the spectrum is gross anatomic deficiency as seen in conditions such as epispadias or bladder exstrophy.

Therapy depends on the underlying disease and the individual social needs of the patient and family. Some conditions resulting in incontinence are best managed by reassurance, some require medication, some require bladder neck closure and creation of a catheterizable channel (e.g., Mitrofanoff conduit), and some require complex total surgical reconstruction. The consistent creation of a bladder outlet mechanism that successfully mimics the bladder neck and external sphincter has eluded surgical creativity to date. The Young-Dees-Leadbetter urethroplasty, the artificial urinary sphincter, and the bladder neck/proximal urethral slings with all of their variants have been wonderful innovations, but none has been ideal.

In 1938, Murless[1] used an injection technique to treat female incontinence, but the method used a sclerosing agent injected into the anterior vaginal wall. In 1955, Quackels[2] injected paraffin attempting to improve periurethral closure. Berg[3] in 1973 and Politano[4] in 1982 used polytetrafluoroethylene (polytef) mixed equally with glycerol to create an injectable paste. With clinical experience, success was reported in 73% of women with stress incontinence[5] and 66% of men with postprostatectomy incontinence.[4] These early successes were not harbingers of a new era of incontinence therapy, however. Malizia and colleagues[6] pointed out that polytef can migrate and travel from the site of periurethral injection to lodge in lungs, kidneys, spleen, and brain. This concern led to the restriction of the use of polytef in this role, and established the subsequent requirement that all substances proposed for this use in the future be analyzed for migration and biocompatibility. Since that time, other materials have been developed and applied to injection therapy, but overall results have not been significantly improved.

The use of bulking agents in pediatric practice has had limited application. The theory behind their deployment is straightforward and simple. Normal lower urinary tract function is based on three principal elements: (1) a compliant bladder that stores urine at an adequate volume at safe pressures; (2) a continence mechanism that remains effective as the volume of stored urine accrues and during stress; and (3) a volitional on-and-off valve, which allows socially appropriate drainage of the bladder. Bulking agents have had their main application in cases of structural urinary incontinence where the second element (the continence mechanism) is faulty.

The theory that “bulking up” can be effective depends on the concept that the urothelium lining the bladder neck and proximal urethra normally coapts and seals the potential space of the urethral lumen. The wet surfaces of the urothelium adhere to each other to provide resistance against leakage. When the bladder neck and proximal urethra at rest are widely separated, incomplete coaptation may allow urine to leak out. Injection of a bulking agent under the urothelium that inflates or elevates the urothelium may increase the coaptation surface area, increasing the functional length of the urethra and bladder neck. The longer the functional length, the more energy it takes to overcome the resistance to push a bolus of urine through the urethra. The subepithelial bulk also brings the potentially coapting structures closer together. These hypotheses are simplistic and mechanistic and physiologically naive, but provide a starting point to understanding the sophisticated bioengineering of the urinary tract (Fig. 60-1).[7] For some patients, intravesical/periurethral bulking results in continence, although its success is unpredictable. Injectable bulking agents work effectively in about one third of selected patients with myelomeningocele and in more than half of selected patients with exstrophy/epispadias.[8]

DIAGNOSIS OF INCONTINENCE

Understanding urinary incontinence in children requires a complete evaluation. As a starting point, a structured “elimination interview” queries the nature and severity of the incontinence (diurnal, nocturnal, fecal) with quantitative analysis.[9] An incontinence symptom index for pediatrics has been developed and validated by Nelson and colleagues.[10] This tool and others may offer more objective methods of evaluating the degree of incontinence and the efficacy of therapies. Imaging studies should include ultrasonography of the kidneys and bladder and voiding cystourethrography. Urodynamic studies are essential for all patients with neurogenic incontinence, bladder exstrophy, and posterior urethral valves to determine better the respective contributions of the bladder and bladder neck to incontinence.

OTHER TREATMENT OPTIONS

Most anomalies in childhood requiring surgical repair for incontinence have a combination of defects in bladder storage and sphincter function. The therapeutic options for improving sphincteric function are limited: increase outflow resistance, create a new sphincter mechanism, or close off the bladder. Bulking agents can be best judged by comparison with other treatment options available for pediatric anatomic incontinence. The ideal treatment would be minimally invasive, would be very effective, and would not affect lifestyle.

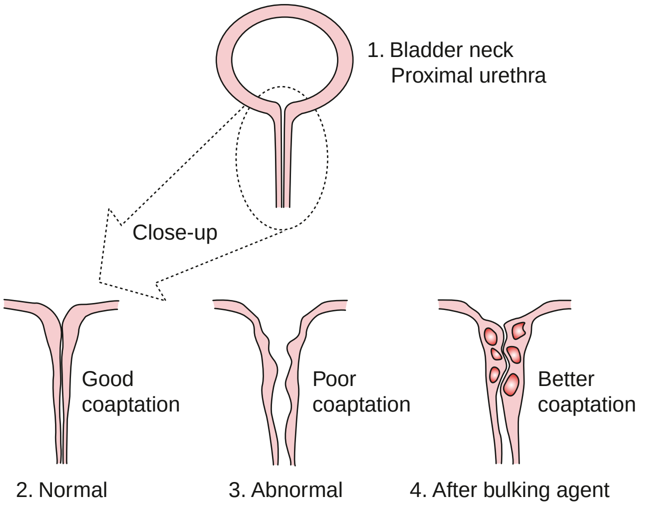

Figure 60-1 Injection of a bulking agent can improve bladder neck coaptation.

The cost should be reasonable, and future treatment options should not be closed off. Other factors to bear in mind are the appropriateness to the patient's body, growth potential, and life expectancy (Table 60-1).

Surgical options that increase urethral resistance should not be considered unless one is certain that bladder compliance and storage are safe. A procedure that increases resistance to surges in abdominal pressure (as measured by the Valsalva leak point pressure) in the wrong patient (i.e., a patient with a hostile bladder) may cause more harm than benefit. Correction of low-pressure leakage without recognizing a poorly compliant bladder would lead to inadvertent and unwanted increases in bladder storage pressures that ultimately threaten the upper tracts.[11]

Gormley and associates[12] reported in 1994 on the pubovaginal sling procedure for the control of urinary incontinence in children. Success rates of 92% were reported in children with type III stress incontinence and adequate bladder capacity and compliance. The disadvantage of the sling procedure includes difficult access to the small pediatric vagina necessitating an abdominal approach. Patients not already performing intermittent catheterization risk a period of prolonged urinary retention. Postoperative detrusor instability is another hazard.[13] In boys, the tight space between the rectum and the prostate makes the puboprostatic sling a challenging procedure with increased morbidity. Were these the only concerns, the procedure would still be popular, but the prostatic urethra is difficult to compress or coapt.[14]

Bladder neck reconstruction or, more correctly, reconfiguration, such as the Young-Dees-Leadbetter procedure, Kropp procedure, or bladder neck closure with alternative access via a continent appendicovesicostomy (Mitrofanoff principle), can also provide continence. Bladder neck reconfiguration increases resistance, which leads to a state of complete continence, but also to the loss of the ability to relax and open the bladder neck volitionally. These patients typically require intermittent catheterization, but the reconfigured urethra can be difficult to navigate, requiring emergent bladder decompression. The reconfiguration process can "consume" a substantial portion of the bladder with a significant loss of bladder volume, and augmentation may be or should be a concomitant procedure. Bladder stones, upper tract deterioration, bladder rupture, and reoperation rates of greater than 50% all have been reported.[15,16]

Table 60-1 Ideal Bulking Agent for Incontinence

Delivery Method
Minimally invasive
Outpatient
Repeatable
Minimal sequelae—does not prevent other options in the future
Wide applicability to various body sizes and shapes
Shallow learning curve
Cost-effective
Material Properties
Nonimmunogenic
Nonmigratory
Minimal inflammation
Durable
Ideal viscosity—thick enough to stay put after injection, thin enough to be easy to inject
Cost-effective

The artificial urinary sphincter has been used successfully in children since 1985 with continence rates of greater than 80%.[17-19] Reoperation rates in these series ranged from 20% to 59% because of mechanical problems, surgical complications, and changes in bladder behavior owing to unappreciated poor bladder compliance before placement. Eventual reoperation would be a logical expectation in most children given the realities of growth and time. Roth and coworkers[20] found 25% of children with artificial sphincters developed radiologic evidence of urinary tract deterioration, urinary retention, or impaired bladder compliance.

ENDOSCOPIC BULKING AGENTS AND METHODS OF APPLICATION

Contemporary bulking agents are composed of organic and synthetic compounds. Nonorganic materials include polytef (Teflon), silicone paste (Macroplastique), bioglass, and detachable membrane systems. Organic bulking agents comprise autologous substances such as fat, chondrocytes, collagen, and bladder smooth muscle cells. Bridging the gap between organics and synthetics are biodegradable materials made from naturally occurring compounds such as Deflux, a highly viscous gel composed of dextranomer microspheres mixed with nonanimal stabilized hyaluronic acid (a constituent of cartilage).[21]

The underlying principle with these materials is to provide bulk at the bladder outlet and proximal urethra to increase urothelial coaptation. Three basic methods deliver the bulking agent to the area of interest: transurethral, periurethral, and antegrade (Fig. 60-2). All three options are possible in girls. In boys, delivery is chiefly transurethral or antegrade. Regardless of the approach used, care should be taken to minimize the number of needle punctures to avoid extravasation of the bulking agent. Meticulous needle placement and technique are critical factors. Trsinar and associates[22] considered faulty technique a key factor in the early failure of endoscopic collagen treatment of vesicoureteral reflux.

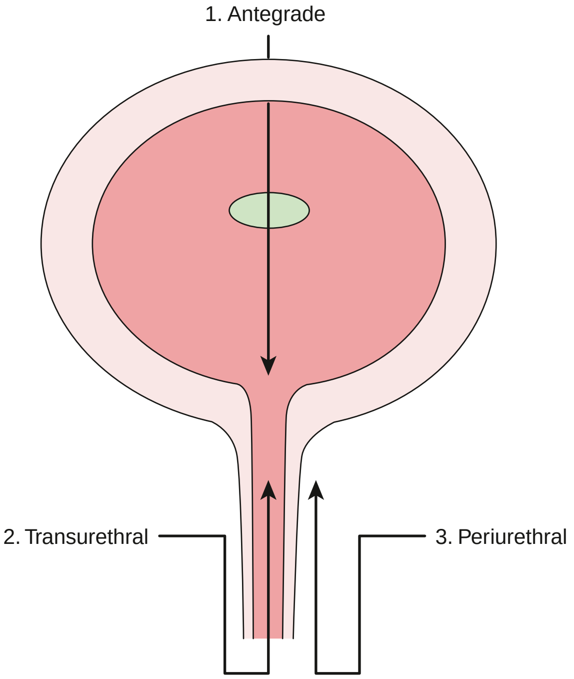

Figure 60-2 Three basic methods deliver the bulking agent to the area of interest: transurethral, periurethral, and antegrade.

Transurethral Method

We prefer transurethral delivery via cystoscopes with a 5F working channel and a 0- or 12-degree lens. A good rule of thumb is to employ the smallest size sheath feasible in boys and the largest reasonable sheath in girls. The patient is placed in the dorsal lithotomy position. General anesthesia is usually needed. In adults and very mature children, intraurethral instillation of 2% lidocaine jelly may be sufficient. Additional lidocaine can be injected into the subepithelial space before administering the bulking agent to provide additional anesthetic and to help establish the appropriate tissue planes. Bulking agent is administered in the 3- and 9-o'clock positions until epithelial approximation is visually established. Care is taken not to pass either the cystoscope or a large-bore catheter during the perioperative period to avoid molding or extrusion of the bulking agent. If prolonged catheter drainage is anticipated, a suprapubic tube may be helpful. Repeat Credé maneuvers often show continence when coaptation has been achieved. Serial injections may be necessary.

Periurethral Method

Some authors advocate periurethral injection in women.[23] After a local anesthetic is injected into the periurethral space and under cystoscopic visualization, the injection needle is guided through the periurethral space until the tip is seen just beneath the urothelium at the 4- and 8-o'clock positions. The tip should be just in the subepithelial space beyond the bladder neck. Bulking agent is administered as described previously until epithelial coaptation is visualized.

Antegrade Method

Prior surgery or poor tissue compliance in the proximal urethra and bladder neck may limit the success of retrograde injection. In these patients, bulking agents can be delivered in antegrade fashion via a suprapubic cystotomy.[24] Visualization can be improved by using two cystoscopes; one in the suprapubic tract and the other through the urethra. The additional view helps to orient and place the bulking material more accurately in the bladder neck.

SYNTHETIC INJECTABLES

Polytef

The modern era of injectable therapy was initiated by the introduction of polytetrafluoroethylene (polytef) formulated in a 50:50 mix with glycerol to form an injectable paste. The mixture decreased the viscosity enough to inject through a fine needle, while still retaining its bulking properties. Polytef has enjoyed good success rates of 73% of women with stress incontinence and 66% of men with postprostatectomy incontinence.[5,25] Despite these favorable results, concern was raised about polytef use in humans. Polytef particles incite a vigorous inflammatory reaction whose fibrosis can create a mass effect potentially affecting future surgery. Fibrosis leading to urinary obstruction has been reported.[26] Subsequent studies with polytef have shown phagocytosis by macrophages resulting in migration of particles into the reticuloendothelial system.[6]

Human and animal studies have shown migration and granuloma formation in lymph nodes, spleen, lungs, kidneys, and brain.[27] No specific harm, disease, or pathologic condition has been identified to be a result of this migration. Puri[28] reported on a large of group of children treated with polytef for vesicoureteral reflux. No complications arising from particle migration were shown after 10 years of follow-up. Although the significance of particle migration remains unclear, there is a reluctance to use polytef in children, and formal approval its use for this purpose was never obtained from the U.S. Food and Drug Administration (FDA).

Macroplastique

Macroplastique is a 40:60 mixture of particulate silicone with a povidone gel (polyvinylpyrrolidone) carrier, which creates a thick yellow injectable paste. Henly and coworkers[29] examined particle migration of Macroplastique in dogs to ascertain if the same concerns as for polytef existed. They found that migration varied proportionally with particle size. Large particles (>100 μm) remained in place, but smaller particles (<70 μm) migrated. The difference in migration was attributed to the ability of macrophages to engulf smaller particles, but not the larger ones. A histiocytic reaction occurred, but no granuloma formation was seen in response to injections.

European series have reported on the successful use of Macroplastique in incontinent adults. Sheriff and associates[30] reported short-term success rates of 75% and long-term success rates of 48%. Duffy and Ransley[31] reported on 12 boys with epispadias treated with Macroplastique: 3 became dry, 6 improved, and 3 were unchanged. More recently, Guys and associates[32] reviewed 44 children with spina bifida who received bladder neck injections with Macroplastique; 21 of these patients had undergone prior bladder neck reconstruction, and 15 had prior augmentation cystoplasties. Prior surgical procedures did not affect the ability to inject Macroplastique effectively. The results were comparable with other types of agents: 34% became dry, 25% improved, and 41% unchanged.

Macroplastique also has been used in the endoscopic treatment of vesicoureteral reflux. Dodat and associates[33] injected nearly 300 children with 454 ureters and reported a greater than 90% resolution rate regardless of grade of reflux or cause. The advantages of Macroplastique are cited in comparison with cross-linked collagen, and include better fluid consistency, absence of retraction, and no local or distant inflammatory reaction.

Silicone implants have been reported to be associated with human rheumatologic disorders.[34] Although a causal link has never been established, Macroplastique has not been approved by the FDA and has not found widespread acceptance in the United States.

Silicone Membrane Systems

Concern over particle migration, resorption of bulking agent, and potential immunologic sequelae spurred the development of endoscopically delivered balloon implants to provide bulk. Barrett and colleagues[35,36] described the use of saline-filled silicone spheres for the treatment of female incontinence. Atala and coworkers[37,38] expanded on the idea with detachable self-sealing membrane balloons placed endoscopically into the subepithelial space and inflated with a nondegradable filler material (polyvinylpyrrolidone) to provide tissue bulk. Although these systems have not shown evidence of migration or inflammatory reaction, they have had performance issues related to atrophy of overlying tissue, postplacement bladder instability, positioning difficulties, device extrusion, and device rupture.[36]

Bioglass

Ceramic biomaterials have been used as a bone mass replacement in orthopedic surgery. Stability and lack of reactivity led to investigation for urologic use.[39] Walker and colleagues[39] examined injectable bioglass, a bioactive ceramic composed of silicon oxide, calcium silicate, calcium oxide, and calcium fluoride. Tissues are bound with minimal inflammatory response by the attachment of collagen fibers to the glass surface with no evidence of toxic effects in vitro or in vivo. Studies in pigs and rabbits found a stable implant with no evidence of particle migration or inflammatory response.[39] Although it may have potential application, to date bioglass has been limited to orthopedic and periodontal applications. One concern is that any subsequent surgery in an area injected with bioglass may encounter a dense bioglass-collagen scar.

Polysaccharide Microsphere (Deflux)

Deflux is a mixture of dextranomer microspheres (cross-linked dextran polysaccharides) suspended in an absorbable solution of sodium hyaluronan, a naturally occurring viscous polysaccharide. The microspheres are nonimmunogenic, do not migrate (particle size >80 μm), and are biodegradable through hydrolysis. Long-term bulk is achieved through the recruitment of fibroblasts to the injection site with subsequent native collagen deposition. Clinical trials with Deflux used in the treatment of vesicoureteral reflux have found success rates of 70%.[40,41] Lottmann and colleagues[42,43] found that children and adolescents treated with Deflux for severe incontinence owing to sphincteric incompetence had reasonable results; 50% were dry or improved with no long-term side effects after follow-up of up to 7 years. A cost analysis from Europe found that the cost of Deflux injection therapy is comparable to other methods of treating stress urinary incontinence, such as tension-free vaginal tape.[44] Although not more expensive, the overall cost is not cheap, being around $1200 per 1-mL syringe.

NONAUTOLOGOUS ORGANIC THERAPIES

Collagen

Of all of the bulking agents, only collagen has been approved by the FDA and has a long clinical history. Collagen-based products have been in use for decades; resorbable sutures and hemostatic agents are their primary applications. Injectable collagen is a highly purified suspension of bovine fibrillar collagen and is currently available in a solution of 95% type I collagen mixed with 5% collagen with the trade names of Contigen, Zyderm, and Zyplast. The collagen is harvested from bovine dermis. It is solubilized, and the immunogenic potential of the material is strongly reduced by proteolytic digestion and glutaraldehyde cross-linking. Enzymatic digestion removes most of the antigenic sites on the material, and cross-linking inhibits resorption. The polymerization further reduces the effect of the remaining antigenic sites. Compared with non–cross-linked collagen, the glutaraldehyde-treated form is associated with substantially lower risk of hypersensitivity (<1%).[45] There are no reports of injected collagen migration, and the inflammatory response is minimal.

Shortliffe and colleagues[46] reported on 17 adult patients who had urinary incontinence after pelvic surgery and had a 53% dry or improvement rate. McGuire and Appell[47] found an 83% cure or improvement rate in 30 men and a 94% cure or improvement rate in 35 women treated with collagen. Wan and associates[7] reported on the first use of collagen in eight children for the treatment of incontinence; 63% were cured, and 25% were improved. Four years later, an extended series reported on 32 additional pediatric patients with long-term follow-up.[8] After 4 years, 22% were cured, and 54% were improved. Greater improvement and postoperative satisfaction occurred in patients with the exstrophy-epispadias complex (92% patient satisfaction) than in patients with spina bifida (50% patient satisfaction). Others have also shown the tendency for collagen to be most effective in exstrophy-epispadias patients.[48] Speculation is that the wide variability in patient response relates to the degree of epithelial flexibility or rigidity in the bladder neck and proximal urethra.

Concern has been raised about the potential for injected bovine collagen to be resorbed with a subsequent need for retreatment. Comparison of our results with the original study group by Wan and associates[7] showed that after a mean follow-up of 4.5 years, the overall cure or improvement rate remained durable at 86%, indicating that the response to collagen is sustained. The cross-linking of collagen with glutaraldehyde makes the collagen resistant to collagenase, inhibiting resorption. Our experience has also shown that collagen administration does not impair subsequent open surgical reconstruction. Other potential disadvantages of collagen include cost. Currently, injectable collagen costs about $300 per 3-mL syringe. Multiple syringes are used per session.

Despite the widespread use of collagen-based products, concern remains over the possible immunologic sequelae of their use. It has been suggested that an immune response to bovine collagen injected into a patient with no previous autoimmune disease might trigger the development of an immune reaction against the recipient's own collagen.[49] Cukier and associates[50] reported that the incidence of autoimmune diseases such as polymyositis and dermatomyositis was statistically increased among collagen-treated patients compared with the expected incidence in the general population. In contrast, other reports show no clear disease association with the use of collagen products.[51,52]

Elson[52] hypothesized that a sequence of events must occur for an autoimmune disease to develop from injectable collagen: (1) the patient must develop anti–bovine collagen antibodies, (2) these antibodies must cross-react with human collagen, and (3) the human collagen antibodies must produce a reaction in muscle tissue. Of this possible sequence, only the development of anti–bovine collagen antibodies has been shown to occur. The increased anti–bovine collagen antibody levels have not been shown to predispose to developing an autoimmune disease, and the anti–bovine collagen antibodies remain species-specific, and do not cross-react with human collagen.[53]

Patients should be counseled about the possibility of delayed hypersensitivity reaction to the collagen itself. Stothers and Goldenberg[54] reported on 337 women who were treated with collagen and who had at least a 1-year follow-up. Delayed skin test reactions were found in 0.9%, and two of these patients had new systemic arthralgias. Ironically, the initial skin test to check for hypersensitivity may be a sensitizing event. Whether there is a long-term significance of collagen implants remains to be determined. Considering the wide use of collagen-based products, however, for most patients collagen exposure does not pose a major health hazard.

AUTOLOGOUS ORGANIC THERAPIES

The concept of using a patient's own cells as a bulking agent has great appeal, especially in children. Such an approach would avoid immunologic concerns of tissue compatibility, particle migration, or inflammatory response. Additionally, autologous tissue could potentially have a cost advantage depending on the expense of tissue processing.

Autologous Fat

Plastic surgeons have used adipose tissue as free grafts for decades.[55] The principal barrier to the use of autologous fat as a bulking agent is the loss of volume over time, especially in large-volume injections. A large-volume injection is essentially a free graft dependent on inosculation and imbibition for graft survival. To date, fat injections for the treatment of urinary incontinence have been disappointing.[56] Greater than 70% of female patients treated with fat injection for urinary incontinence showed partial resorption of the implant after 22 months. Continence rates of 64% have been achieved, but only by providing repeat injections every 3 months.[57] A lack of efficacy relative to other bulking agents and the very high rate of resorption have limited the role of autologous fat as a urologic bulking agent.

Autologous Collagen, Chondrocytes, and Bladder Muscle Cells

Research has been conducted to investigate the feasibility of using other forms of autologous tissue in this role. Cendron and associates[58] used a rabbit model to prove the stability of autologous collagen after subepithelial injection into the bladder. It remains to be shown how best to harvest and cultivate sufficient quantities of the autologous collagen for practical use. Autologous chondrocytes are promising as bulking agents because chondrocytes possess the ability to form viable cartilage. Chondrocytes are harvested from the auricular surface, and the cells are grown and expanded in vitro for 5 to 8 weeks. The chondrocytes are mixed with dry alginate powder to form an injectable gel. Clinical trials have shown that it can be applied as an injectable substance in the treatment of vesicoureteral reflux.[59,60]

Caldamone and Diamond[60] found that the substance achieved an immediate overall correction rate of reflux of 86% of injected ureters with some patients requiring three injections. At 1 year, the rate of reflux declined to 70%, and a concern of further late relapse was raised. Finally, more recent animal and in vitro studies have suggested that bladder muscle alginate complexes may be another biocompatible possibility.[61,62] All of these avenues of research may yield practical treatments, but await breakthroughs in the field of tissue engineering and until then remain tantalizing possibilities.

Table 60-2 **Summary of Bulking Agents**

Type	Comments
Synthetics	
Polytef	Concerns about migration and absorption; particles appear elsewhere in the spleen, lungs, brain, and liver
Macroplastique	Little migration when only larger particles are used, but concerns exist about possible link between silicone and later rheumatologic disorders
Silicone membrane balloons	Technical difficulties, durability
Bioglass	Limited human genitourinary experience; unknown effect on any later procedures
Deflux	Polymer synthesized from natural components, FDA approved for use in treating vesicoureteral reflux
Nonautologous Organics	
Collagen	FDA approved for treatment of incontinence, variable results
Autologous Organics	
Autologous fat	Lacks durability
Autologous collagen, chondrocytes, bladder muscle	Need practical method of harvesting and cultivating tissue in sufficient quantities

FDA, U.S. Food and Drug Administration.

CONCLUSION

Successful management of pediatric anatomic urinary incontinence is a challenge. The first step in successful treatment is defining the various causes of failure of continence. When bladder capacity and compliance are favorable, and incontinence is due to an incompetent outlet, bulking agents can provide a minimally invasive therapeutic option in achieving continence.

The quest for the ideal injectable agent continues (Table 60-2). The host's reaction to the agent seems to be crucial in determining long-term safety and durability. Newer substances avoid problems with particle migration, granuloma formation, and inflammatory response. Cost and durability remain obstacles. Tissue engineering technology may offer materials that would be biocompatible and provide durable continence.

We have taught residents to have a healthy wariness of any surgical reports that are composed of less than triple digit patients and double digit years of follow-up. In an evolving world of changing materials and surgical techniques, such skepticism cannot become nihilism or cynicism. Therapeutic medical science is not a static endeavor. We should be open to innovation, but at the same time strive to base our therapeutic decisions on the best techniques, materials, and evidence available. Should a particular method or approach gain consensus, we must continue to seek improvement and refinement with equal vigor, knowing that our best solutions today will be replaced by better solutions tomorrow.

REFERENCES

For complete list of references log onto www.expertconsult.com

SECTION 3

ASSOCIATED INTESTINAL ABNORMALITIES

CHAPTER 61

FECAL INCONTINENCE IN PEDIATRIC UROLOGY

Padraig S. J. Malone

Problems with the gastrointestinal and urinary tracts frequently coexist. They may be part of a complex congenital abnormality, they may share a common cause such as a neuropathy, or an abnormality in one system may affect the other.[1] The gastrointestinal abnormality often manifests with chronic constipation or fecal incontinence or both; the main causes of fecal incontinence are listed in Table 61-1. The pediatric urologist must be aware of these gastrointestinal anomalies and be conversant with their clinical presentation, management, and prognosis. Patient care is usually shared with other specialists, such as pediatric surgeons or pediatricians. The urologist should be able to initiate and supervise simple treatment, however, and with the development of new surgical techniques, the urologist also may be responsible for the operative management of fecal incontinence, particularly during lower urinary tract reconstruction.

PATHOLOGY

Cloacal anomaly is a rare condition that accounts for approximately 15% of high anorectal malformations in girls. In this condition, a common channel connects the genital, urinary, and gastrointestinal tracts (Fig. 61-1), and long-term urologic management is required in many of these patients for the associated bladder dysfunction, chronic renal failure, and gynecologic abnormalities.[2-5] Approximately 50% of these patients have normal bowel function; patients without normal bowel function present a complex management problem involving the genitourinary and gastrointestinal systems.[2,4] Cloacal exstrophy is another rare anomaly in which abnormal colonic function is always present. A permanent colostomy has been the treatment of choice, but more recently, reasonable fecal continence has been achieved in some patients with an enema program after an abdominoperineal pull-through procedure, provided that a formed stool can be achieved.[6,7] There is a common association of gastrointestinal problems and prune-belly syndrome; short bowel syndrome, megacolon, and Hirschsprung's disease all are described. These conditions may cause chronic constipation or fecal incontinence or both.[8]

Of children with spina bifida, 84% have a neuropathic bladder and bowel, causing urinary and fecal incontinence.[9,10] Only 24% of adults with spina bifida are continent, and 30% have urinary and fecal incontinence.[9] Similar problems are also encountered in children with other forms of spinal dysraphism.[11] Chronic constipation severely affects the bladder, leading to incomplete emptying, worsening incontinence, and urinary tract infections. Bladder and bowel management must be addressed simultaneously for the best results to be achieved.

Long-term fecal incontinence is a common feature in children with anorectal malformations.[10] Urinary tract anomalies occur in 20% of patients with low lesions and 50% of patients with high lesions.[12-14] One of the most common problems is vesicoureteric reflux, but it has become clear that many patients also have a neuropathic bladder. In two more recent studies, neuropathic bladder was found in 11% and 25% of patients with high anorectal malformations, and greater than 90% of these patients had partial or complete sacral agenesis.[15,16] The most common abnormality is detrusor overactivity, but acontractile bladders have also been seen in a few patients.[15] In 1999, these abnormalities were grouped together under the term *ARGUS* (*A*no*R*ectal, *G*enito*U*rinary, and *S*acral).[13] Postoperative urinary tract complications may also occur after the treatment of anorectal malformations. These include urethral strictures after division of the rectourethral fistula or a posterior urethral diverticulum if fistula excision is inadequate. These diverticula may manifest many years after surgery with infection and pelvic pain, often as a result of stone formation. Some patients present with terminal dribbling and incontinence.

Chronic idiopathic constipation, with or without soiling, also has a significant effect on bladder function, causing enuresis, urinary tract infection, or a combination of both. In children with chronic constipation, vesicoureteric reflux is reported in 20%, hydronephrosis is reported in 31%, an elongated urethra is reported in 40%, and a misshapen bladder is reported in 66%.[17] Urodynamic studies have also shown detrusor overactivity in patients with chronic constipation.[18,19] A few patients with chronic constipation and no urinary symptoms also had detrusor overactivity, and these findings improved after treatment of the constipation.[20] Several other studies have also noted the association between constipation, enuresis, urinary tract infection, and acute urinary retention, but with no supporting urodynamic data.[21-23] It has been suggested that the distended rectum presses on the bladder wall and produces a bladder outflow obstruction, which causes detrusor overactivity. Aggressive treatment of the constipation alone can cure enuresis and urinary tract infection.[19,20,22]

CLINICAL ASSESSMENT

A careful history and examination are required to differentiate between enuresis or encopresis (or both) and true urinary or fecal incontinence (or both). In most cases, the former can be expected to improve given time and reassurance, but incontinence requires specific investigation and treatment.

Table 61-1 **Causes of Fecal Incontinence**

Structural
Sphincter trauma
Anorectal malformations
Anal stenosis
Dysfunctional
Hirschsprung's disease
Chronic diarrhea
Chronic constipation and overflow
Neuronal intestinal dysplasia
Segmental colonic dilation
Neuropathic
Spina bifida
Spinal dysraphism
Sacral agenesis
Spinal trauma
Spinal tumors
Transverse myelitis
Spinal cord ischemia
Sacrococcygeal teratoma
Neuropathic bowel
Generalized neurologic diseases

History

A detailed history is required to identify the cause of fecal incontinence. Abnormalities noted during the antenatal or early postnatal period may explain the cause. A developmental history with dates of milestones reached is important. Chronic constipation must be excluded because this is the most common cause of soiling. Details of the number of times stools are passed and whether they are liquid, soft, normal, or hard may indicate whether chronic constipation or overflow fecal incontinence is to blame. Rectal sensation may be lost with a neuropathic bowel or with chronic constipation and a megarectum. Any medication that may affect bowel function must be noted. The ability to hold on to stool but not flatus implies a degree of sphincter weakness that may be due to a generalized neurologic condition or a more localized problem with anal sphincter innervation or muscle abnormality.

Examination

A careful examination of the genitourinary, gastrointestinal, and neurologic systems is vital to avoid missing subtle abnormalities. Initially, the patient is asked to walk to assess gait, which, if abnormal, would suggest an underlying neurologic abnormality. The abdomen is examined for fecal loading, distention, or a palpable bladder. Ideally, the urinary stream should be examined. The back is examined for signs of spinal dysraphism or spina bifida occulta, and palpated down to the coccyx to assess for normal sacral and coccygeal development. If sacral agenesis has occurred, the buttocks are flattened, and the gluteal cleft is short (Fig. 61-2). Perineal examination is vital to assess the normal appearance and position of the anus and the external genitalia. Perineal sensation and the anocutaneous reflex are tested. Rectal examination is performed to assess anal tone and to exclude fecal impaction. A careful neurologic examination of the lower limbs is performed.

INVESTIGATIONS

If there is suspicion of a spinal abnormality, anteroposterior and lateral films of the vertebral column are indicated. If a sacral anomaly is suspected, spinal ultrasonography can be performed in children up to 1 year of age because the vertebral

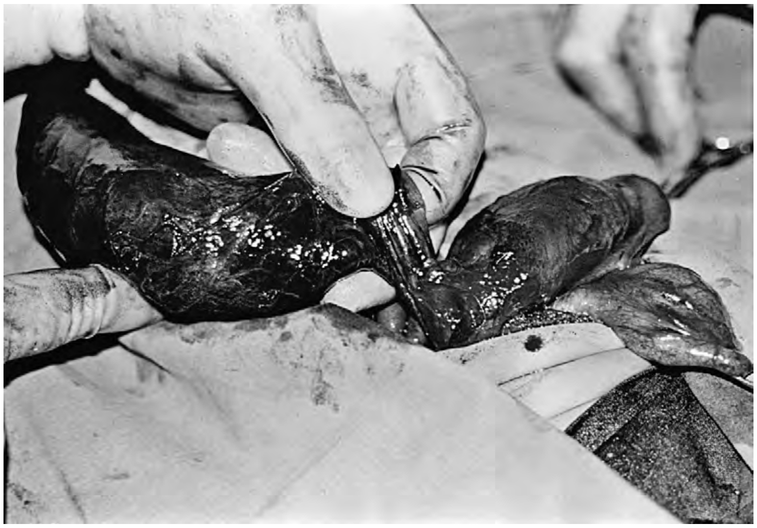

Figure 61-1 Operative findings in cloacal anomaly. The rectum, vagina, and bladder combine to form a common channel.

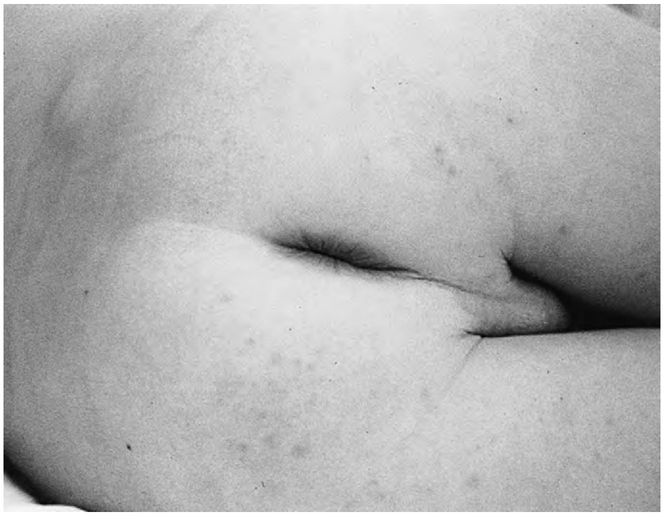

Figure 61-2 Surface appearance of sacral agenesis. Note the flattened buttocks and short gluteal cleft.

arches have not ossified. After this age, magnetic resonance imaging (MRI) clearly shows the presence or absence of spinal abnormality.

In patients with anorectal malformations, investigations should follow the recommendations of Boemers and colleagues (Fig. 61-3).[13] If the sacrum is radiographically normal, there is unlikely to be any congenital intraspinal abnormality, and further investigation is not usually warranted. In the neonatal period, radiographs should be taken early to avoid the sacrum's being obscured by bowel gas. Ultrasonography of the genitourinary tract should be performed 48 hours after birth. Bladder wall thickness and the diameter of the posterior urethra in boys may indicate the site of the rectourethral fistula or indicate a neuropathic disorder.

Micturating cystourethrography should be performed in all children to investigate the possibility of vesicoureteric reflux. The micturating phase of the study may show the site of a rectourethral fistula. In many patients, flow of the contrast material into the rectal pouch can be observed, providing information about the level of the fistula. Reflux into the seminal vesicles and the vas deferens may also be detected. Contrast material introduced into the vagina in girls may outline the anatomy of anorectal malformations. When the patient is approximately 3 months old, videourodynamics should be performed to assess lower urinary tract function. Damage to the nerves supplying the lower urinary tract has been observed after posterior sagittal anorectoplasty, especially in boys with rectourethral fistulas, and repeat videourodynamic studies may be required after surgery. More complex radiologic investigations such as MRI and computed tomography may be useful in patients in whom neurologic examination is abnormal.

Further investigations such as electromyography can help identify specific neurologic disorders that can affect the bowel, bladder, and sphincters. Anal manometry can add additional information to clinical findings, but there is a significant overlap between what is considered normal and what is considered abnormal, and this may not assist in diagnosing the disorder. Shandling and Gilmour[24] described the measurement of the force required to extract a balloon from the rectum. Ambulatory rectal manometry may offer further information. Persistence of high-amplitude colonic waves may be seen in the neorectum after pull-through and may be associated with fecal incontinence.[25]

If sphincter damage is likely transanal, ultrasonography can identify areas of sphincter damage that may be amenable to surgical repair. MRI can also provide useful information about the anal sphincter and pelvic floor. Colonoscopy does not often provide much further information, unless there is coincidental inflammatory bowel disease. Contrast and colonic transit studies may be useful to identify abnormal areas in the colon, particularly areas associated with overflow incontinence after surgery in which isolated segmental colonic dilation may occur.[26,27] Rectal biopsy specimens should be obtained if Hirschsprung's disease is suspected.

TREATMENT OF INCONTINENCE AND CONSTIPATION

The management of constipation in childhood was detailed in an excellent monograph by Clayden and Agnarsson[28] in 1991, and its principles still hold true today (Table 61-2).

Laxatives and Stool Softeners

Before any treatment regimen is begun, the bowel must be cleared initially if there is gross constipation. This can be achieved by using a stool softener such as docusate sodium (formerly dioctyl sodium sulfosuccinate) initially, followed by agents such as senna or sodium picosulfate to produce evacuation. Enemas and manual evacuation are occasionally required at this stage. After the initial colonic emptying is produced, the regular use of stool softeners and addition of extra fluid and fiber to the diet are required. In children, fruit and green fiber are better than large amounts of bran. Other stool softeners include lactulose and the bulking agent methylcellulose. Regular emptying is established with laxatives such as senna, bisacodyl (Dulcolax), and sodium picosulfate. It is important that laxatives be used for a sufficiently long period, usually 1 year or longer in children with idiopathic constipation.

A similar program is applicable to patients with neuropathic bowel or anorectal malformations and should be combined with bowel training. This program should start as early as possible to avoid the development of a megarectum, which, once acquired, decreases the likelihood of successful conservative treatment.[29] When the child is old enough to cooperate,

Figure 61-3 **A,** ARGUS (*A*no*R*ectal, *G*enito*U*rinary, and *S*acral) protocol, an algorithm for initial neurologic screening of neonates with an anorectal malformation (ARM). **B,** Initial management of structural urologic anomalies *(1),* intraspinal abnormality and tethered spinal cord syndrome *(2),* and neurogenic lower urinary tract dysfunction *(3).* CIC, clean intermittent catheterization; DMSA, dimercaptosuccinic acid; IVP, intravenous pyelogram; MAG3, mercaptoacetyltriglycine; PSARP, posterior sagittal anorectoplasty; PSARVUP, posterior sagittal anorectoplasty and vaginourethroplasty; VCUG, voiding cystourethrogram; VUR, vesicoureteric reflux. (From Boemers TM, Beek FJ, Bax NM. Guidelines for the urological screening and initial management of lower urinary tract dysfunction in children with anorectal malformations—the ARGUS protocol. *BJU Int.* 1999;83:662-671.)

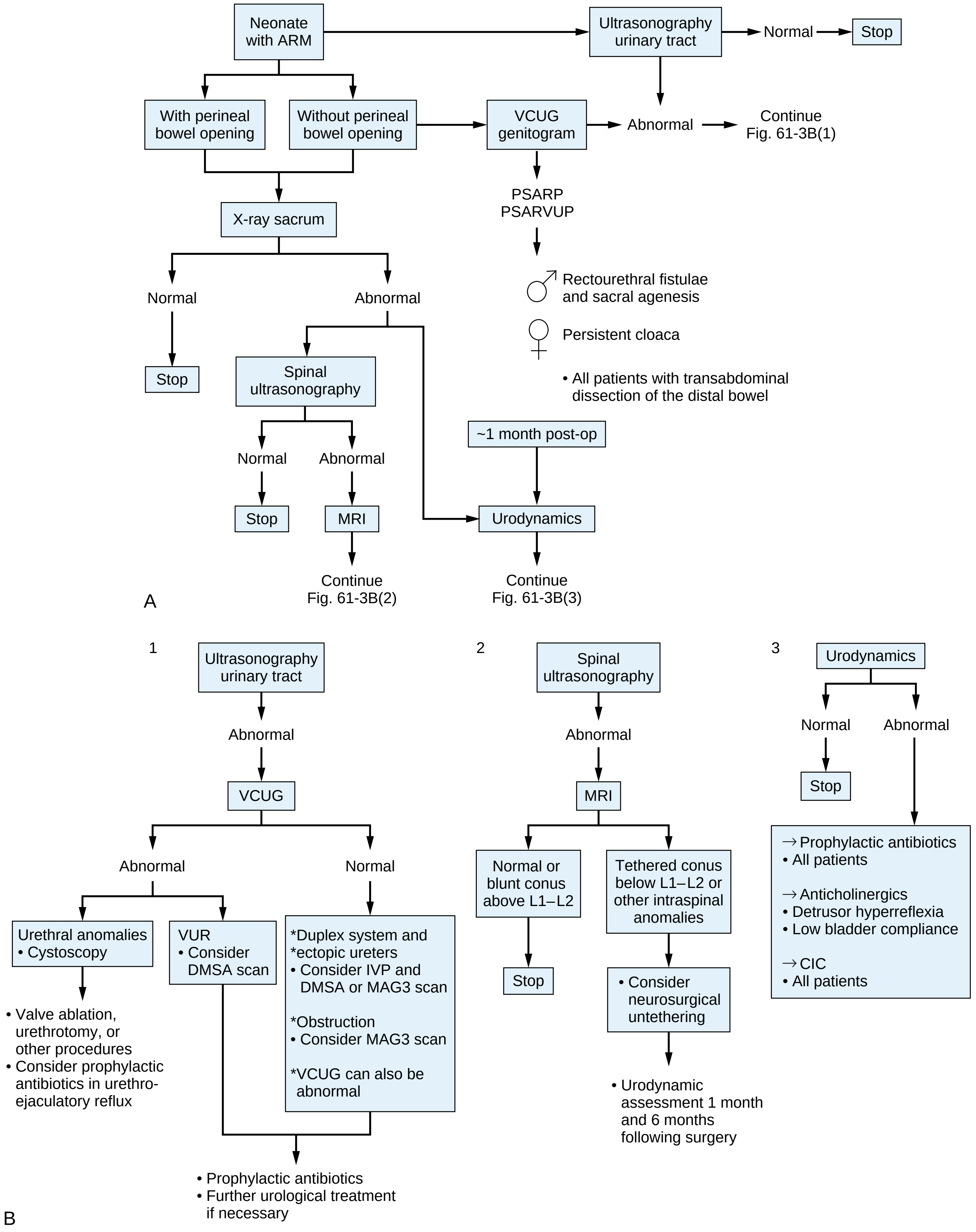
Neonate with ARM
Ultrasonography urinary tract
Normal
Stop
With perineal bowel opening
Without perineal bowel opening
VCUG genitogram
Abnormal
Continue Fig. 61-3B(1)
X-ray sacrum
PSARP
PSARVUP
Normal
Abnormal
♂ Rectourethral fistulae and sacral agenesis
♀ Persistent cloaca
• All patients with transabdominal dissection of the distal bowel
Stop
Spinal ultrasonography
~1 month post-op
Normal
Abnormal
Stop
MRI
Urodynamics
Continue Fig. 61-3B(2)
Continue Fig. 61-3B(3)
A
1
Ultrasonography urinary tract
Abnormal
VCUG
Abnormal
Normal
Urethral anomalies
• Cystoscopy
VUR
• Consider DMSA scan
*Duplex system and
*ectopic ureters
• Consider IVP and DMSA or MAG3 scan
*Obstruction
• Consider MAG3 scan
*VCUG can also be abnormal
• Valve ablation, urethrotomy, or other procedures
• Consider prophylactic antibiotics in urethro-ejaculatory reflux
• Prophylactic antibiotics
• Further urological treatment if necessary
2
Spinal ultrasonography
Abnormal
MRI
Normal or blunt conus above L1–L2
Tethered conus below L1–L2 or other intraspinal anomalies
Stop
• Consider neurosurgical untethering
• Urodynamic assessment 1 month and 6 months following surgery
3
Urodynamics
Normal
Abnormal
Stop
→ Prophylactic antibiotics
• All patients
→ Anticholinergics
• Detrusor hyperreflexia
• Low bladder compliance
→ CIC
• All patients
B

Table 61-2 Management of Constipation

Explain problem fully
Support child and family
Establish effective toileting routines
Use minimal therapeutic input
Ensure complete evacuation of retained stools
Maintain regular bowel movement
Monitor progress

From Clayden G, Agnarsson U. *Constipation in Childhood*. Oxford, England: Oxford University Press; 1991.

he or she is taught to push against a closed glottis. In patients with chronic constipation or with anorectal malformations, or in neuropathic patients with a positive anocutaneous reflex, bisacodyl suppositories or various enema solutions stimulate relaxation of the anal sphincter and reflex contraction of the rectum within 30 minutes and can produce excellent colonic emptying. They are best given soon after a meal to capture the gastrocolic reflex.

Biofeedback

If rectal sensation is present, some patients benefit from biofeedback with the use of a rectal pressure manometer. The child can see the effect of muscle contraction displayed on a monitor. This approach seems to be most successful for patients with anorectal malformations in which there is some preservation of the nerves supplying the anus and rectum.[27,30] Reports of using biofeedback for patients with spina bifida have been varied. In a small series of patients with myelomeningocele, several patients achieved voluntary bowel movements, but others have not reported such good results.[31-33] Biofeedback works best in patients who have spinal cord lesions below L2, and who have two or more bowel movements a day. In this group, biofeedback resulted in a greater than 50% reduction in the frequency of incontinence.[34] In patients with neuropathic bowel and anorectal malformation, the conservative measures described previously may control constipation, but fecal incontinence often persists, and the only treatment method that can be used is timed mechanical colonic emptying (Table 61-3).

Table 61-3 Causes of Persistent Fecal Incontinence

Lack of rectal sensation
Abnormal colonic motility
Inadequate sphincter mechanisms

Timed Mechanical Colonic Emptying

Manual Evacuation

Manual evacuation, with or without laxatives, is a common technique used in the long-term management of neuropathic patients. In patients with a negative anocutaneous reflex, the aim is to produce a bulky stool that aids peristalsis and is easy to remove from the rectum. Most patients continue to soil to some degree, however, and they remain dependent on others to perform the evacuation. For these reasons, it is no longer a popular approach.

Table 61-4 Principles of Antegrade Continence Enema Procedure

Colonic emptying produces fecal continence[35]
Colonic emptying can be achieved by antegrade irrigation[38]
Mitrofanoff principle facilitates intermittent catheterization[39]

Enemas

Enemas have been the mainstay of treatment for years for patients with neuropathic bowel. In 1987, Shandling and Gilmour developed the enema continence catheter.[35] The catheter is inserted into the rectum, and a balloon is inflated to aid retention. Initially, excellent results were obtained, but the long-term compliance declined to 50% after 30 months.[36] In addition, many patients with neurologic diseases or spina bifida were unable to administer the enema independently, which inevitably led to a reduction in compliance. The development of the enema continence catheter showed, however, that complete colonic emptying can produce fecal continence. This led to the development of the antegrade continence enema (ACE) procedure in 1989 (Table 61-4).[37]

The combination of these principles, applied to the colon, provided continent intermittent catheter access to the cecum or proximal colon for the administration of antegrade enemas while the patient sat on the toilet. This produced colonic emptying and fecal continence. The preliminary series was reported in 1990[37]; subsequently, numerous reports have been published, and the procedure is now widely practiced around the world.[40-45] Many modifications have been introduced since the original description[46] to simplify the procedure and to reduce the high complication rates initially reported.[47] In this chapter, we concentrate on the techniques in current use, patient selection and preparation, the enema regimens, and the most recent results.

PATIENT SELECTION AND PREPARATION

All conservative measures must be tried before resorting to ACE. The underlying diagnosis is important because it influences the success rate. Patients with a neuropathic bowel and anorectal malformation had a success rate of 73% compared with 38% for patients with chronic idiopathic constipation.[48] These results were mirrored by the wider experience in the United Kingdom, where a success rate of 91% was also reported for patients with Hirschsprung's disease.[41] The age at operation was also important; there was a 70% failure rate for patients younger than 5 years compared with 24% for children older than 5 years, a highly significant difference.[48] This was independent of the underlying diagnosis, and it probably reflected the inability of a child younger than 5 years to sit on a toilet for up to 1 hour.

Patient and caregiver motivation is vital. Most series reveal a rate of noncompliance leading to abandonment of the ACE stoma of approximately 10% to 20%.[49] Some centers advocate involvement of a psychologist in all cases undergoing an ACE procedure.[50,51] Detailed preoperative counseling and continued postoperative support, ideally provided by a nurse specialist, are essential to ensure adequate and continued motivation, without which the ACE is doomed to failure. It is an advantage to introduce the potential patient to a patient in whom the ACE is successful, along with his or her family.

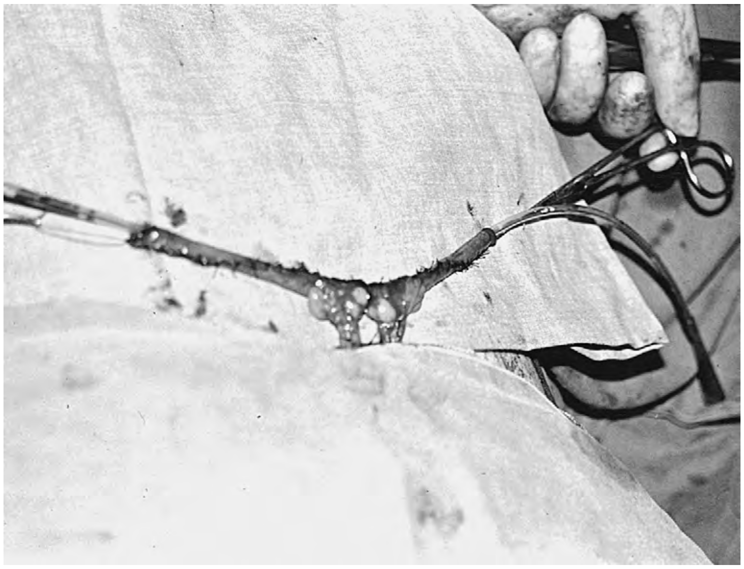

Figure 61-4 The "full Monti"—two tubularized segments joined to form a long catheterizable conduit. (From Sugarman ID, Malone PS, Terry TR, Koyle MA. Transversely tubularized ileal segments for the Mitrofanoff or Malone antegrade colonic enema procedures: the Monti principle. *Br J Urol.* 1998;81: 253-256.)

OPERATIVE TECHNIQUE

An aggressive preoperative bowel preparation is essential to facilitate the initial postoperative enema. Prophylactic antibiotics are always used, and the conduit is left intubated for 4 weeks postoperatively before starting intermittent catheterization.

The original description of the ACE involved detaching the appendix from the cecum, reversing it, and reimplanting it back into a submucosal tunnel in the cecum, to produce continence.[37,46] The procedure has now been significantly modified in numerous ways to simplify the procedure and to reduce the high complication rates initially reported.[47] The current techniques are described elsewhere by Malone.[52]

If the appendix is being used at the level of the cecum, it is no longer necessary to disconnect it. It can simply be folded onto the cecum, and a cecal wrap performed around it as a valve mechanism, the in situ appendix.[52,53] When the antireflux mechanism has been constructed, the cecum or colon is sutured to the back of the anterior abdominal wall to ensure that the conduit is not lying free in the peritoneal cavity because this can lead to kinking and difficulties with catheterization. This is the approach recommended when a combined Mitrofanoff procedure is also required,[54] with the Mitrofanoff being constructed from either a split appendix[55] or a Yang-Monti conduit.[56,57]

The Yang-Monti is an ingenious technique that transversely tubularizes a 2-cm segment of ileum to produce a catheterizable conduit approximately 7 cm in length, with the valvulae conniventes running in the longitudinal direction of the conduit, which facilitates catheterization. Both ends of the conduit are free of mesentery, and this makes the creation of the antireflux mechanism easy. When a Monti conduit is used, a submucosal tunnel is created along one of the taeniae and wrapped around it, as in the original description of the ACE.[37] If the patient is obese, it is possible to use two segments of ileum and produce a 14-cm conduit that is long enough for almost any patient (Fig. 61-4). Experience with this technique is encouraging, and it is the procedure of choice when the appendix is unavailable.

There is controversy as to whether any continence maneuver is required at all, and some authors now recommend that the tip of the appendix be simply excised and brought out to the abdominal wall. Conduit incontinence rates would seem to be slightly higher using this approach, but if a minimally invasive laparoscopic approach is being used, this would seem to offset the slightly increased risk of stoma leakage. If an isolated ACE procedure only is needed, a laparoscopic ACE offers a simple and effective approach.[58,59] Because some of the port sites can be incorporated into the ACE stoma or hidden in the umbilicus, the cosmetic result is usually excellent, with a functional outcome comparable to that of open surgery.

One problem encountered in some patients with the ACE, particularly patients with constipation, is the time it takes for the washout to work. This problem has led to failure and abandonment of the procedure in many patients.[47] In an attempt to overcome this problem, some surgeons have placed a Monti-ACE conduit in the left colon to reduce the length of bowel that has to be washed through and the time taken for washout. Preliminary results with this approach are very encouraging, and in the authors' experience this has salvaged the procedure in five patients in whom an original cecal ACE failed.[60,61] A left ACE should always be considered in all patients with severe associated constipation because the constipation may be due to delayed transit through the colon. A distal ACE is not without its own problems, however, because the late accumulation of liquid mainly in the cecum and sigmoid colon can cause long lasting leakage after enemas following transverse colon ACE.[62]

The other technique worthy of consideration is the use of a cecostomy tube and cecal button. In 1996, Shandling and colleagues[63] described a technique for the percutaneous placement of a cecal tube that could be changed at a later date to a low-profile cecal button (similar to a gastrostomy button), which is used to administer the enema. In a survey of 300 Malone ACE procedures performed in the United Kingdom, 19 cecal buttons were used, and they worked well in most cases.[41] The most common problem encountered in all catheterizable conduits is stomal stenosis in 30% of patients. A cecostomy button, although the results are not perfect, offers a satisfactory alternative to a catheterizable conduit.[64] For patients with recurrent stomal stenosis, it is also possible to leave a button in the conduit after dilation, and this works well.

A new development embracing the principles of minimally invasive surgery and the left sided ACE has occurred

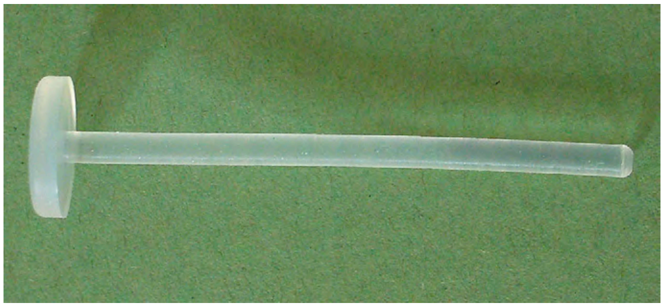

Figure 61-5 The Medicina ACE stopper (Medicina, Adlington, Lancashire, UK).

more recently. After bowel preparation, a colonoscopy is performed, and with the scope in the distal descending colon a colostomy tube is inserted, as one would insert a percutaneous endoscopic gastrostomy—the percutaneous endoscopic colostomy. Washouts can begin the next day, and when the tract has matured, the patient has a choice of keeping the tube, exchanging it for a button, or having a formal conduit created, knowing that the ACE would work, having had a trial of it via the percutaneous endoscopic colostomy. Because of these advances it is now easy to perform simultaneous ACE and Mitrofanoff procedures, offering patients the chance of complete continence for the first time.[51,54,55,65]

There are numerous different approaches to the ACE. If the patient requires a synchronous bladder reconstruction, a formal conduit is constructed using the in situ appendix in the cecum or a left-sided Monti-ACE if constipation is a severe problem. If only an ACE is required, a laparoscopic ACE would be the procedure of choice for cecal placement, or a percutaneous endoscopic colostomy if the patient is constipated, and a left-sided placement is needed. With the adoption of these newer techniques, complications such as incontinence of the conduit or difficulties catheterizing it are decreasing.

The remaining aspect of operative technique is the construction and placement of the stoma. As discussed earlier, the most common complication of ACE is stomal stenosis. In most of these patients, this can be managed with simple dilation, but some require surgical revision. More recent studies have shown no difference in the rate of stoma stenosis comparing the ACE and Mitrofanoff stomas, and the stoma site or the conduit used, appendix or Monti, seems to make no difference.[64,66,67] One study has suggested that the in situ ACE may have lower stenosis rates because the appendiceal blood supply is better preserved.[45]

The initial description of the ACE advocated a cutaneous V flap, but the Ransley VQZ flap (or a modification of it) is now recommended, and this has been shown to reduce stomal problems significantly in the Mitrofanoff procedure.[55,64,68] This stoma uses two separate skin flaps and can be constructed on the abdominal wall or in the umbilicus. Patients are now advised to intubate the stoma twice a day, and this seems to reduce the problems with stenosis. More recently, the author is leaving a Medicina ACE stopper (Medicina, Adlington, Lancashire, UK) in the stoma for the first 6 months, and the initial impression is that this is reducing the stenosis rate still further (Fig. 61-5). These stoppers come in various diameters (10F, 12F, and 14F) and various lengths (15 to 100 mm).

ENEMA REGIMEN

The first enema is given via the indwelling catheter when bowel activity returns, usually around postoperative day 5. Many enema regimens are used in the different centers performing ACE, and patients frequently modify them to suit their own particular needs. One of the most important points is to advise patients not to expect immediate success because an individual regimen usually takes 1 month to establish by trial and error. Many patients experience a degree of rectal leakage within the first few hours of the washout, but this is rarely a major problem.

While the washout regimen is being established, it is vital to maintain regular contact with the nurse specialist. Initially, daily washouts are recommended, but when the patients are comfortable with the procedure, they may attempt to decrease the frequency to alternate days. When a steady state has been achieved, no benefit is gained from interfering with the regimen. It is essential that patients and caregivers be aware of the time commitment that is required and be prepared to devote this time to bowel care because if they do not, the ACE will fail. Because patients have to sit on the toilet for this length of time, one of the complications that has been encountered is pressure sores on the buttocks. It is possible to get padded toilet seat covers, and their use is recommended, particularly for a neuropathic patient with reduced or absent sensation.

The enema given differs from center to center, with most centers in the United Kingdom favoring the use of a stimulant, but enemas in the United States mainly use saline solution or tap water. A common regimen uses a phosphate enema (Fletcher's; Pharmax, Bexley, Kent, United Kingdom). Initially, 50 to 100 mL of enema solution is made with saline solution, and this is rapidly instilled, followed by approximately 500 mL of saline solution. Depending on the response, adjustments are made to the strength and volume of the phosphate up to a maximum of 100 mL of undiluted phosphate enema. Although a few patients achieve successful results with the phosphate alone, most require the additional saline solution lavage. Care must be taken when using phosphate, and the dose needs to be adjusted depending on the age of the child.

If the enema does not produce a result, a second one should not be given because phosphate toxicity may occur if it is retained, and this is a potentially life-threatening complication.[69] If the enema does not produce an immediate result, patients should be advised to wait 1 hour and then perform a further saline solution lavage. If that does not work, the patient should be admitted to the hospital for a retrograde enema and observation. Care must be taken regardless of the agent used because there are anecdotal reports of deaths occurring when too much salt was added to tap water.[70]

Numerous difficulties have been experienced during establishment of the ACE. The most common problem has been pain during the enema, which occurred in 58% of patients. In most patients, the pain settled during the first 3 months. Strategies to reduce pain include reducing the concentration of the phosphate; reducing the rate of the infusion; using an antispasmodic before the enema (Colofac; Solvay, United Kingdom); or changing the enema agent to a licorice root solution, which produces less peristalsis than the phosphate. Three inches of licorice root or 5 mL of commercially available licorice granules are microwaved with 100 mL of saline solution until the mixture boils. It is allowed to cool to room temperature and then diluted with a further 200 mL of saline solution before administration. It is also possible to vary the concentration of the licorice depending on the response and if the patient experiences pain. Numerous patients in the United Kingdom are now successfully using this regimen, which seems to produce much less pain. It is also possible to use many other laxatives, such as bisacodyl or docusate sodium, by instilling them directly into the colon via the ACE.

Table 61-5 Success of Antegrade Continence Enema Procedure Based on Diagnosis

Diagnosis	Complete Success (%)	Partial Success (%)	Failure (%)
Spina bifida	63	21	26
Anorectal	72	17	11
Hirschsprung's disease	82	9	9
Constipation	52	38	38

Data from Curry JL, Osborne A, Malone PS. The MACE procedure: experience in the United Kingdom. *J Pediatr Surg.* 1999;34:338-340.

RESULTS

The results of the ACE have been classified as follows:[48]

Full success: Patient is totally clean, or there is minor rectal leakage on the night of the washout.
Partial success: Patient is clean, but there is significant rectal leakage and occasional major leaks. The patient is still wearing protection, but the situation is perceived by the parent or child to be an improvement from previously.
Failure: Regular soiling or constipation persists, there is no perceived improvement, and the procedure is abandoned, usually to a colostomy.

In 1998, Curry and associates[48] reported on 31 patients with a mean follow-up of more than 3 years. ACE failed in 12 of 31 (39%) patients; this included 5 of 8 patients treated for chronic idiopathic constipation and 1 patient with Hirschsprung's disease. When patients with neuropathic bowel and anorectal malformation were analyzed separately, partial or full success rates were 75% and 70%. In 1999, Curry and coworkers[41] reported on a survey of ACEs performed by members of the British Association of Paediatric Surgeons. They identified 300 cases, and the success rates dependent on the original diagnosis are shown in Table 61-5. The overall success rate, including full and partial success, for this large national series was 79%. More recent studies have shown continued long-term success, even during pregnancy.[71]

Data from several studies of simultaneous combined ACE procedure and bladder reconstruction, including the Mitrofanoff procedure, suggest double continence rates of 95%.[51,54,65,66,72,73] Current evidence requires that a synchronous ACE procedure should always be considered when a patient with fecal incontinence is submitted to bladder reconstruction. The reconstructive urologist is the best individual to manage the bowel because the operative techniques involved are those routinely employed in lower urinary reconstruction, and the infrastructure should be in place for meticulous follow-up. If we adopt this combined approach, we have the ability to enhance the quality of life for these patients.

Numerous publications of studies have assessed the improvements in quality of life objectively, and all have shown significant benefits from the ACE.[43,51,74-76] Shankar and coworkers[74] studied 40 patients using a quality of life improvement score. A score of 5 denoted a perfect result, and the mean score for all patients was 3.5. In another publication from the same unit where there was a mean follow-up of 5.4 years (3.25 to 8.25 years), 82% of 62 patients continued to use their ACE with a mean satisfaction score of 9, with 10 denoting complete satisfaction.[43] Aksnes and colleagues[75] assessed the results of 20 patients 6 months after an ACE procedure. They used numerous validated questionnaires, including the Youth Self Report, Child Behaviour Check List, and Self Perception Profile for Adolescents. They concluded that there were important improvements in self-esteem and psychosocial functions after an ACE procedure. Similarly, Liard and associates[76] published results of the survey of the Malone continent cecostomy to be highly satisfactory in 23 of 28 patients (83%).

There are significant complication rates, however. In addition to the stoma problems already discussed, other complications include wound infection, adhesion obstruction, cecal volvulus, necrosis or kinking of the conduit, and incontinence of the conduit (which occurs in <10% of patients). This is not an exhaustive list.

Sphincter Reconstruction

The use of gracilis muscle to provide a sling to improve fecal continence has been described.[27,77] The muscle is transposed around the anus and is stimulated via implanted electrodes to provide patients with neosphincters. Conflicting results have been reported, with some reports suggesting very poor results[78] and others claiming 50% to 100% of patients achieving satisfactory continence.[79-81] This approach still must be regarded as experimental. An alternative to the gracilis sling is levatoroplasty, with one series reporting improvement in continence in 75% of patients.[82] Artificial anal sphincters also have been used and a successful outcome has been reported in approximately 70% of patients with short-term follow-up.[83,84] Sepsis and rectal evacuatory dysfunction continue to be major problems, however.[27,85]

Electrostimulation

Transcutaneous electrical stimulation has been tried to improve fecal continence in patients with spina bifida, using low-intensity, long-duration nighttime stimulation via patch electrodes. Decreased fecal soiling was reported, with patients describing an improved sensation of pelvic fullness facilitating a better toileting regimen.[86] Sacral nerve stimulation has also been investigated in the management of fecal incontinence, and although the mechanism of action is unclear, the results are encouraging.[87]

CONCLUSION

Provided that the patient is well prepared, it should be possible to achieve urinary and fecal continence in most patients without the use of urostomies and colostomies. Because the reconstructive urologist has the required skills for bladder reconstruction, most are also able to manage the neuropathic bowel, but for more complicated surgery, a colorectal surgeon with an interest in anorectal abnormalities should be involved from an early stage.

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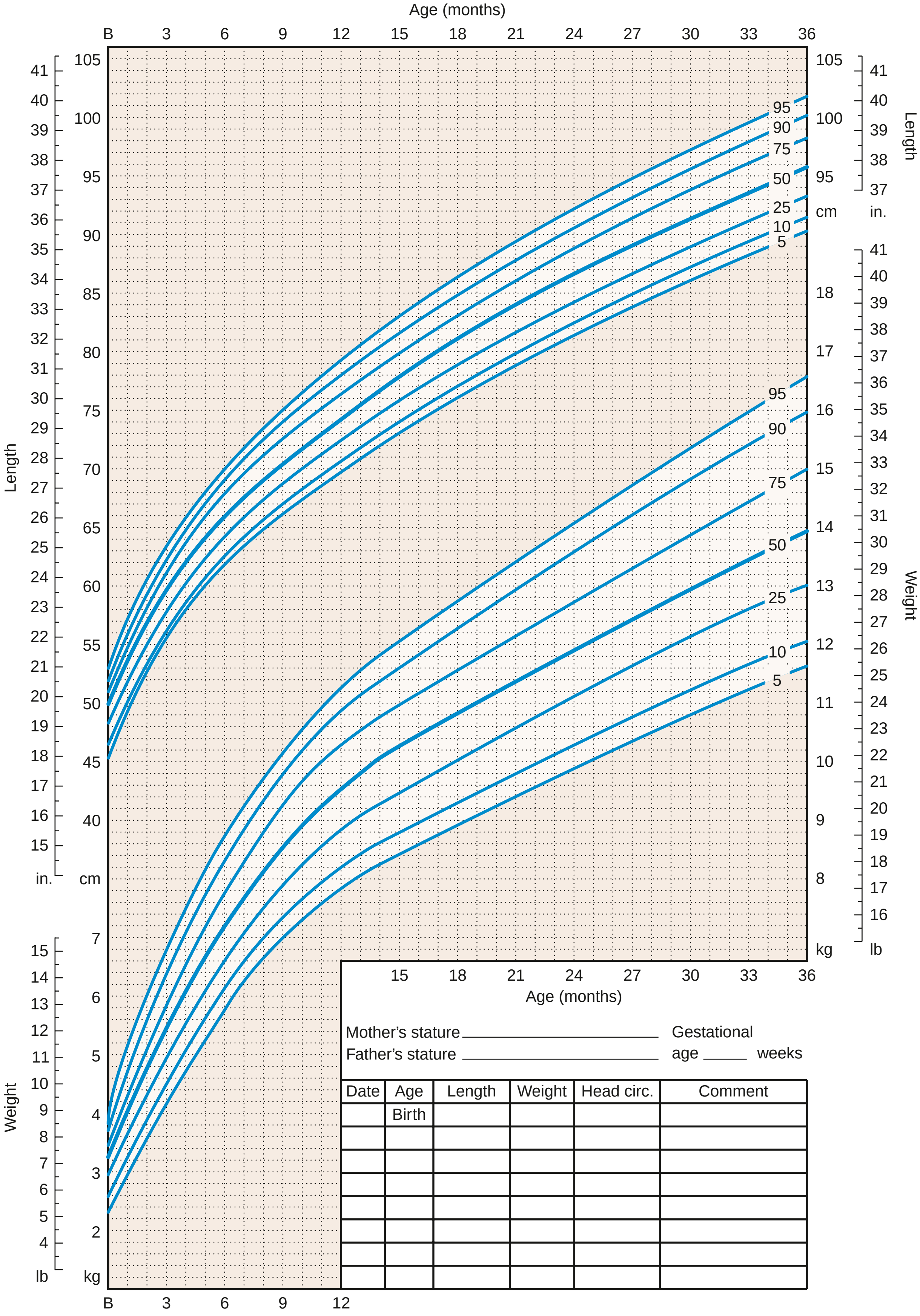
PART XI

APPENDIX

STANDARDS

David B. Joseph

Name ____________________ Record number ______________



Mother's stature ____________________ Gestational

Father's stature ____________________ age _____ weeks

Date	Age	Length	Weight	Head circ.	Comment
	Birth				

Chart 1 Girls: Birth to 36 Months Physical Growth (NCHS Percentiles)*

*Adapted from Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32:607-629. Data from the Fels Longitudinal Study, Wright State University School of Medicine, Yellow Springs, Ohio.

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Name ___________________________ Record number__________________

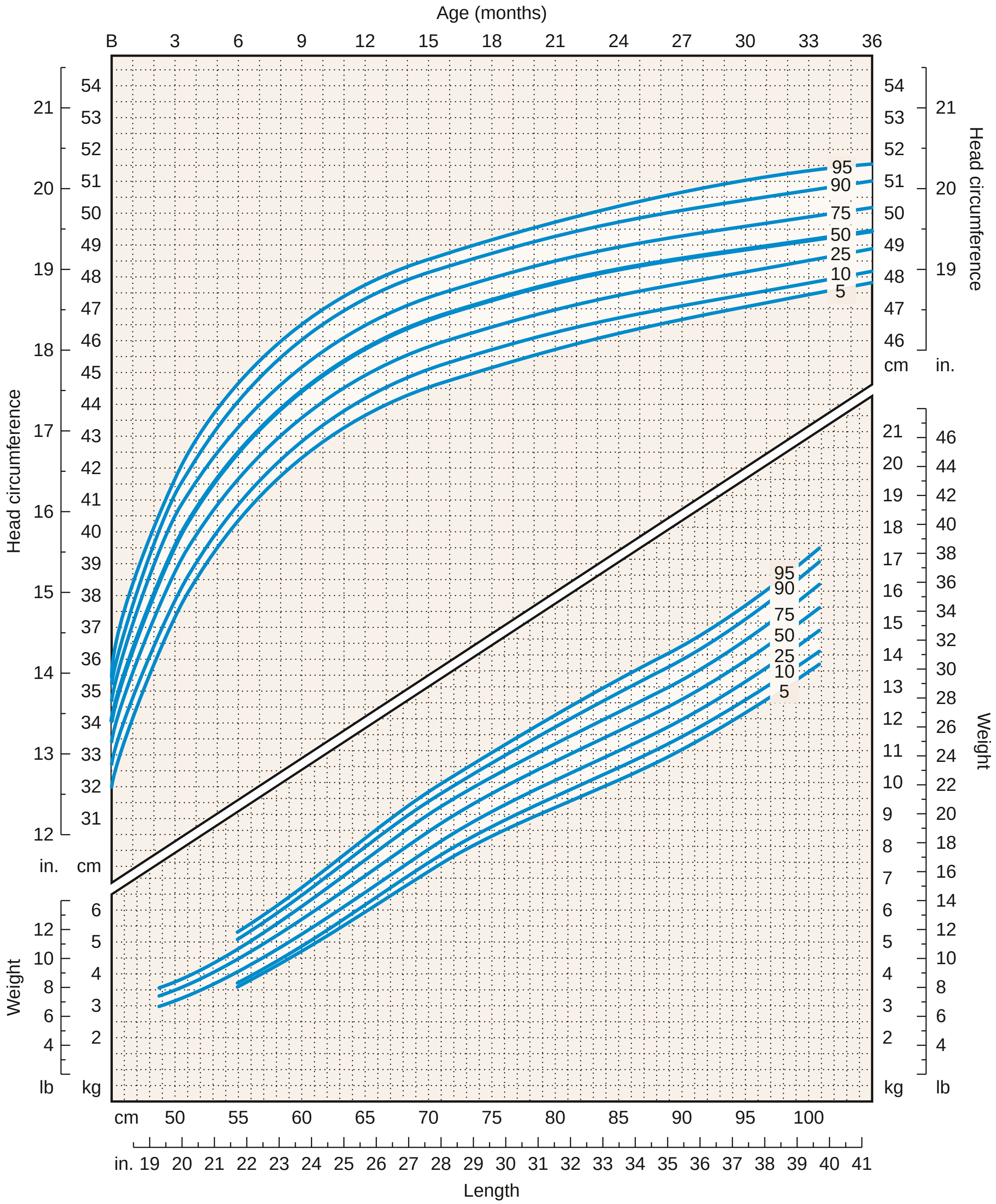

Chart 2 Girls: Birth to 36 Months Physical Growth (NCHS Percentiles)*

*Adapted from Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32: 607-629. Data from the Fels Longitudinal Study, Wright State University School of Medicine, Yellow Springs, Ohio.

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Date	Age	Length	Weight	Head circ.	Comment
	Birth				

Name ______________________ Record number ______________

Mother's stature ____________________

Father's stature ____________________

Date	Age	Length	Stature	Comment

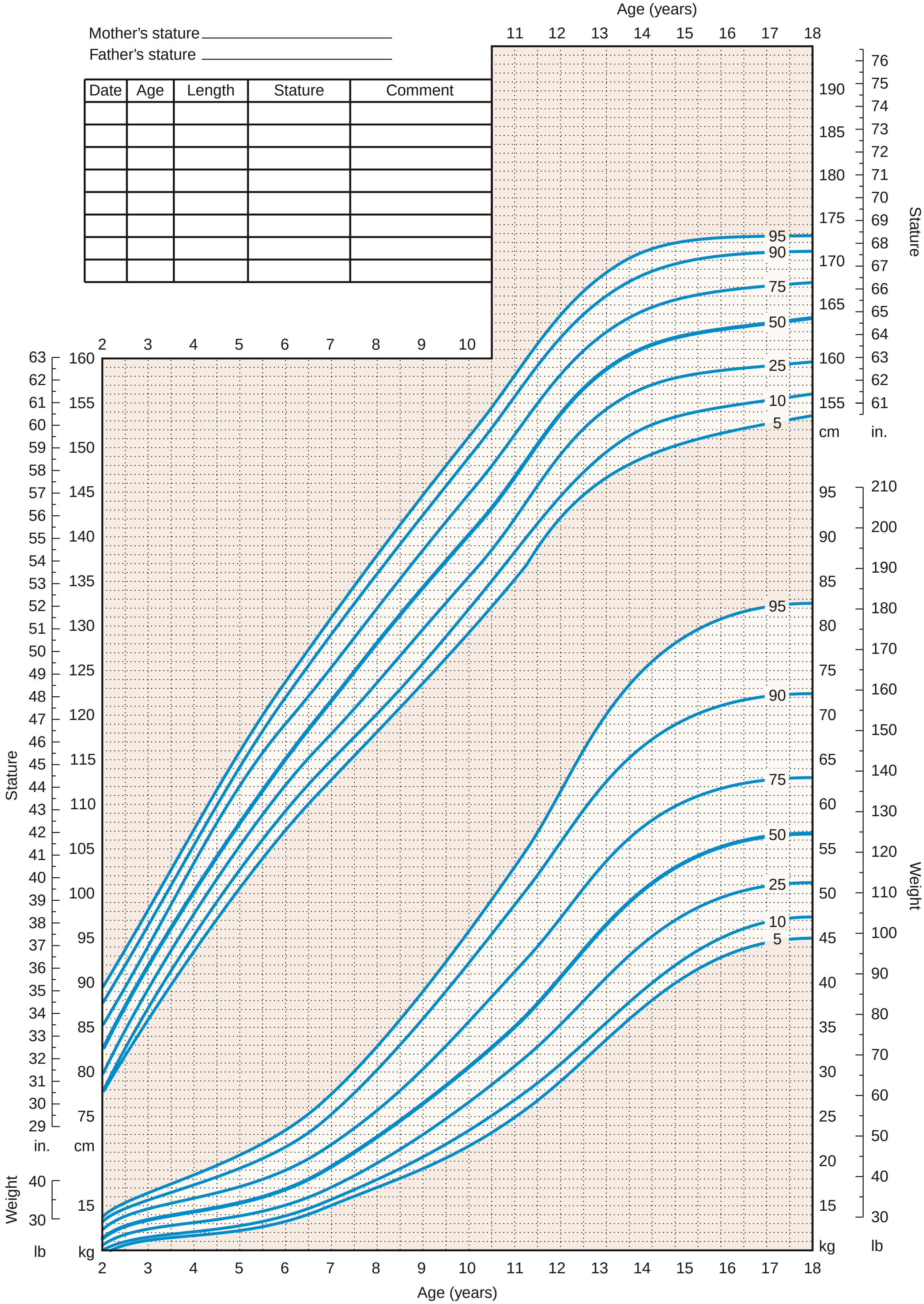

Chart 3 Girls: 2 to 18 Years Physical Growth (NCHS Percentiles)*

*Adapted from Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32:607-629. Data from the National Center for Health Statistics (NCHS), Hyattsville, Maryland.

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Name ______________________________

Record number ______________________

Date	Age	Stature	Weight	Comment

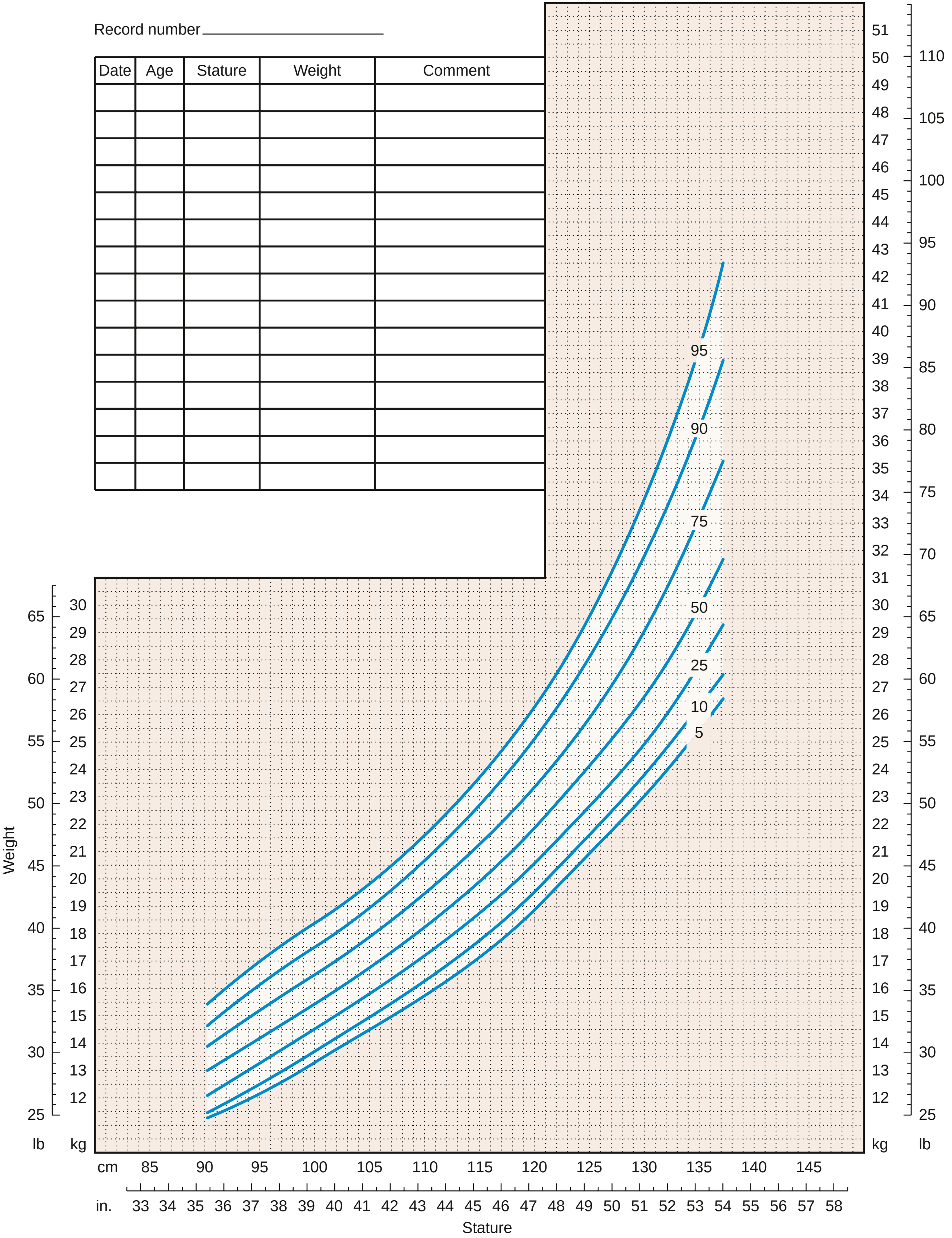

Chart 4 Girls: Prepubescent Physical Growth (NCHS Percentiles)*

*Adapted from Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32:607-629. Data from the National Center for Health Statistics (NCHS), Hyattsville, Maryland.

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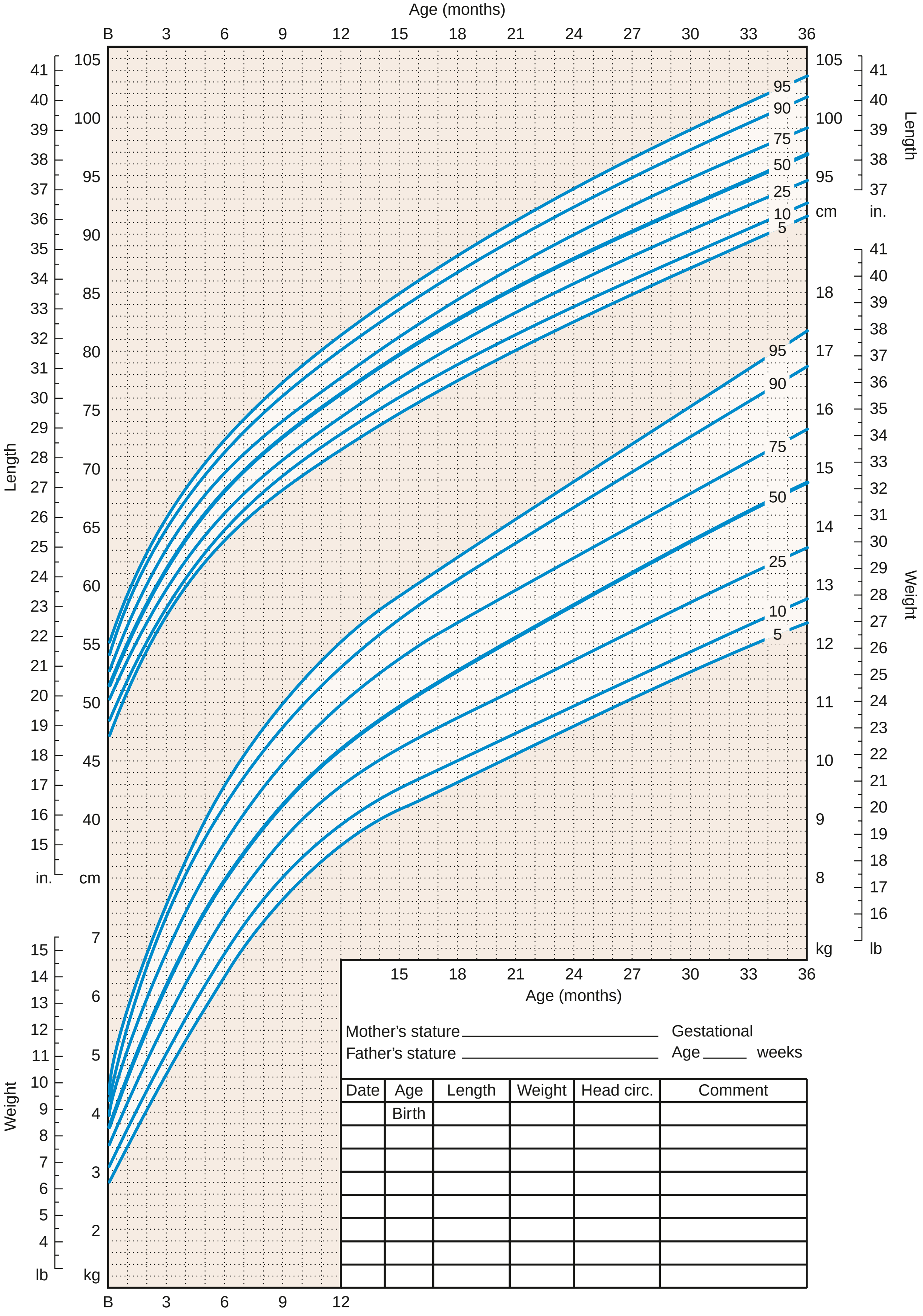
Name ______________________ Record number ______________



Mother's stature ______________ Gestational

Father's stature ______________ Age _____ weeks

Date	Age	Length	Weight	Head circ.	Comment
	Birth				

Chart 5 Boys: Birth to 36 Months Physical Growth (NCHS Percentiles)*

*Adapted from Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32:607-629. Data from the Fels Longitudinal Study, Wright State University School of Medicine, Yellow Springs, Ohio.

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Name ___________________________ Record number _________________

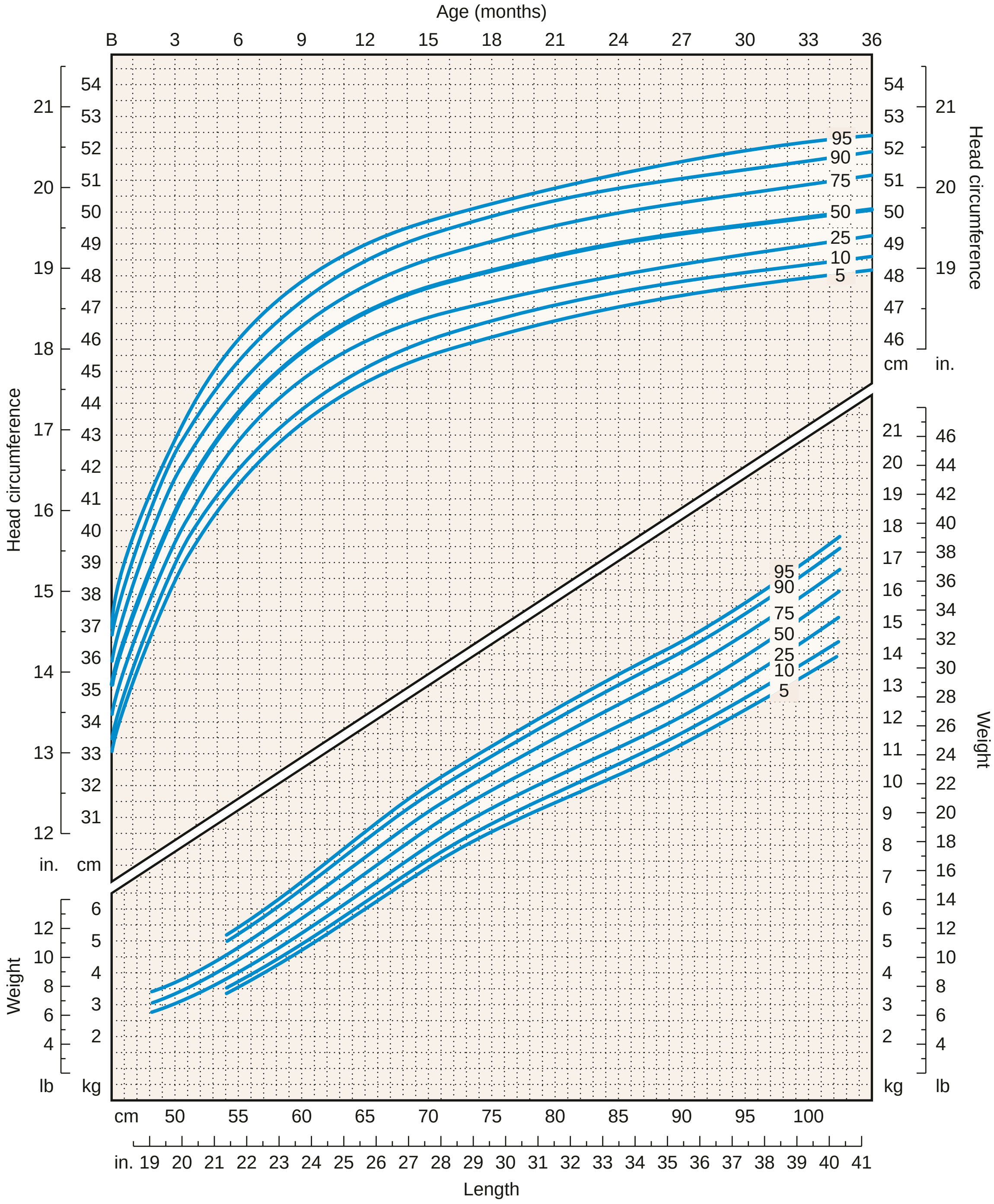

Chart 6 Boys: Birth to 36 Months Physical Growth (NCHS Percentiles)*

*Adapted from Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32:607-629. Data from the Fels Longitudinal Study, Wright State University School of Medicine, Yellow Springs, Ohio.

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Date	Age	Length	Weight	Head circ.	Comment
	Birth				

Name ______________________ Record number ______________

Mother's stature ____________________

Father's stature ____________________

Date	Age	Length	Stature	Comment

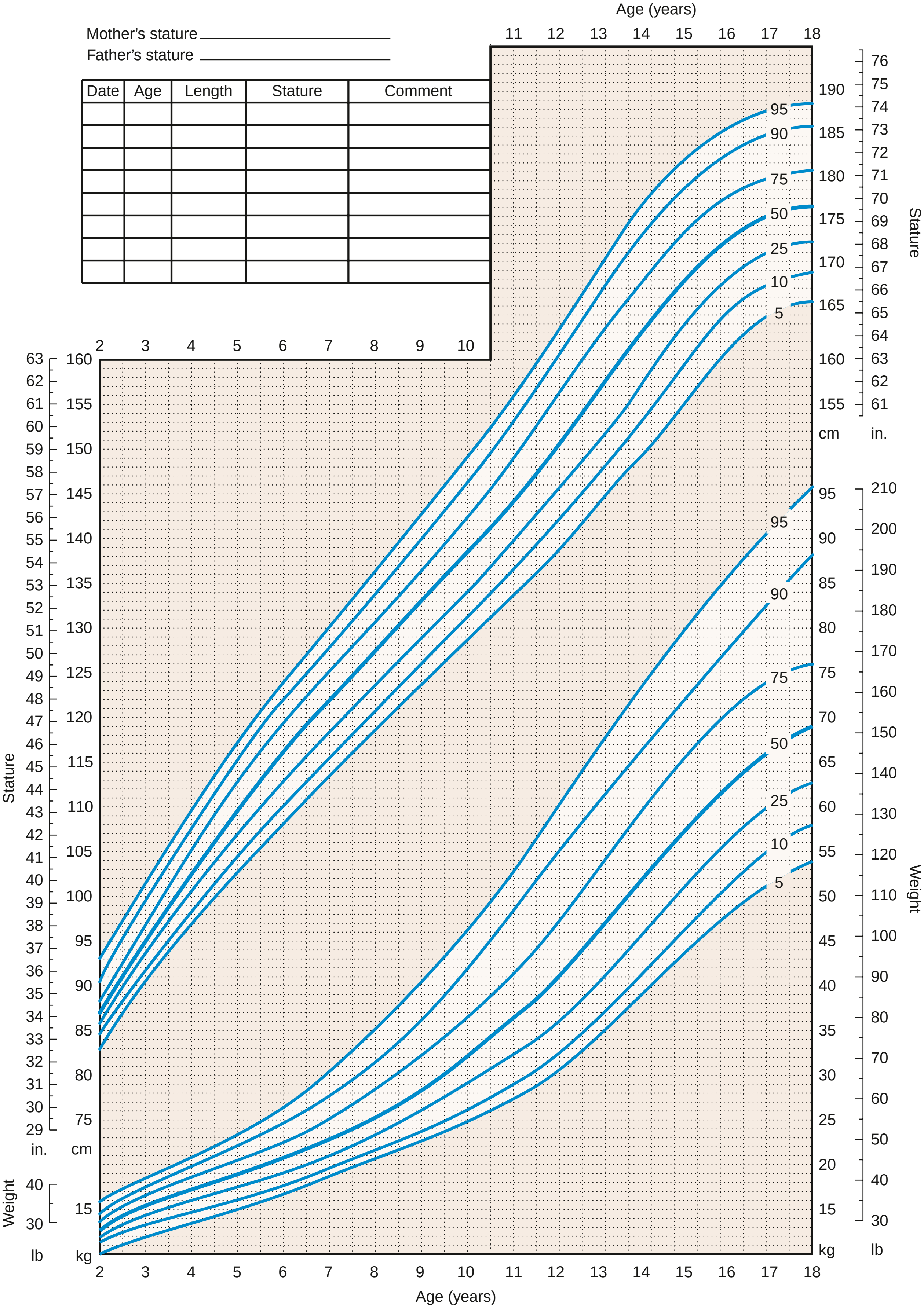

Chart 7 Boys: 2 to 18 Years Physical Growth (NCHS Percentiles)*

* Adapted from Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32:607-629. Data from the National Center for Health Statistics (NCHS), Hyattsville, Maryland.

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Name ______________________

Record number ______________________

Date	Age	Stature	Weight	Comment
	Birth			

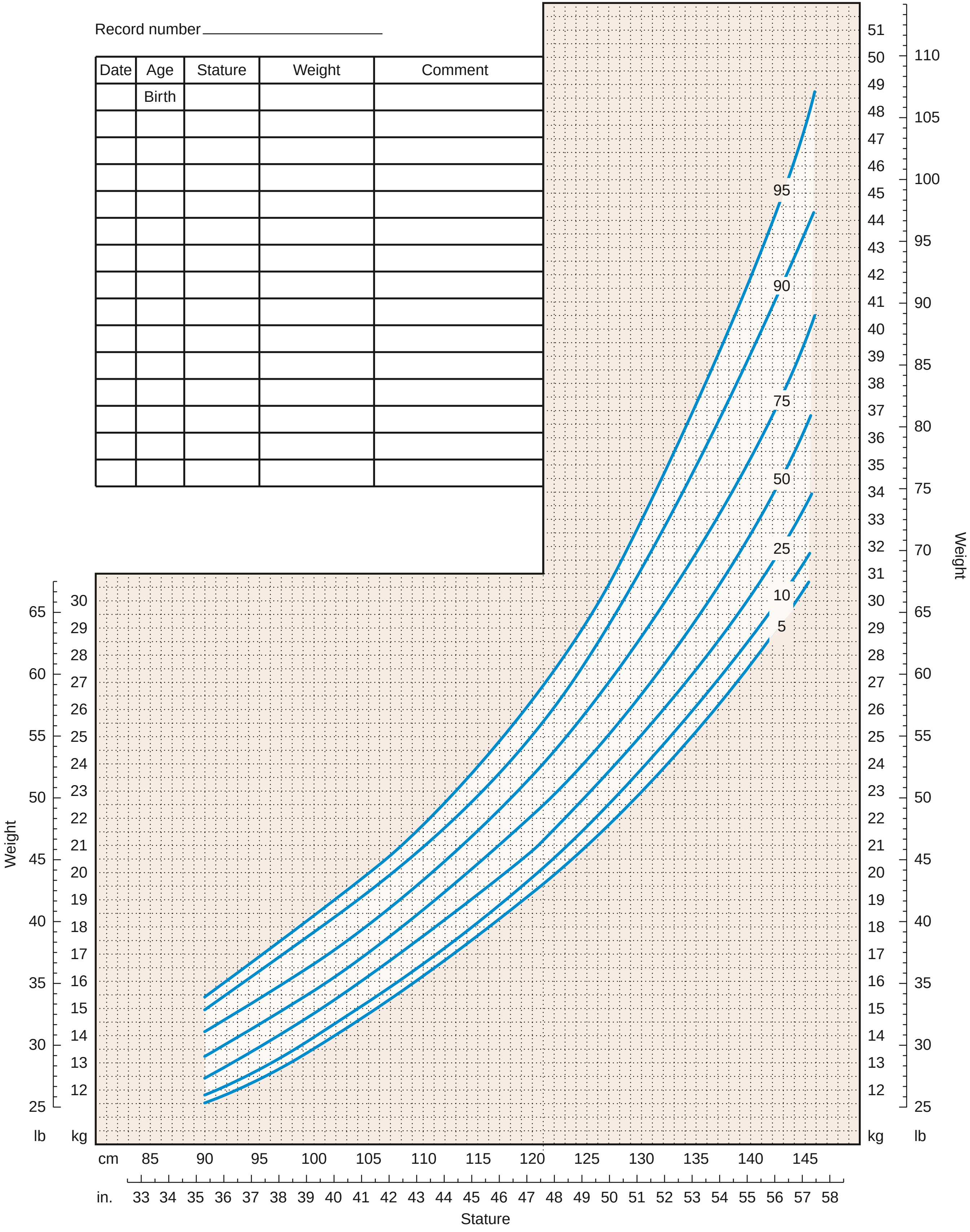

Chart 8 Boys: Prepubescent Physical Growth (NCHS Percentiles)*

*Adapted from Hamill PVV, Drizd TA, Johnson CL, et al. Physical growth: National Center for Health Statistics percentiles. *Am J Clin Nutr.* 1979;32:607-629. Data from the National Center for Health Statistics (NCHS), Hyattsville, Maryland.

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STANDARDS

Hypertension Definitions

Term	Definition
Normal BP	Systolic and diastolic BPs <90th percentile for age and sex
High normal BP*	Average systolic or average diastolic BP (or both) between 90th and 95th percentiles for age and sex
High BP (hypertension)	Average systolic or average diastolic BP (or both) >95th percentile for age and sex with measurements obtained on at least 3 occasions

---

*If the BP reading is high normal for age, but can be accounted for by excess height for age or excess lean body mass for age, such children are considered to have normal BP.

BP, blood pressure.

From Report of the Second Task Force on Blood Pressure Control in Children—1987. *Pediatrics.* 1987;79:1.

Classification of Hypertension by Age Group

Age Group	Significant Hypertension (mm Hg)	Severe Hypertension (mm Hg)
Newborn–7 days	Systolic BP >96	Systolic BP >106
8-30 days	Systolic BP >104	Systolic BP >110
Infants <2 yr	Systolic BP >112	Systolic BP >118
	Diastolic BP >74	Diastolic BP >82
Children 3-5 yr	Systolic BP >116	Systolic BP >124
	Diastolic BP >76	Diastolic BP >84
Children 6-9 yr	Systolic BP >122	Systolic BP >130
	Diastolic BP >78	Diastolic BP >86
Children 10-12 yr	Systolic BP >126	Systolic BP >134
	Diastolic BP >82	Diastolic BP >90
Adolescents 13-15 yr	Systolic BP >136	Systolic BP >144
	Diastolic BP >86	Diastolic BP >92
Adolescents 16-18 yr	Systolic BP >142	Systolic BP >150
	Diastolic BP >92	Diastolic BP >98

BP, blood pressure.

From Report of the Second Task Force on Blood Pressure Control in Children—1987. *Pediatrics.* 1987;79:1.

Mean Renal Length: Normal

Age (yr)	Mean Renal Length (cm)
0.5	6.15 ± 0.67
1	6.65 ± 0.54
2	7.36 ± 0.54
3	7.36 ± 0.64
4	7.87 ± 0.50
5	8.09 ± 0.54
6	7.83 ± 0.72
7	8.33 ± 0.51
8	8.90 ± 0.88
9	9.20 ± 0.90
10	9.17 ± 0.82
11	9.60 ± 0.64
12	10.42 ± 0.87
13	9.79 ± 0.75
14	10.05 ± 0.62
15	10.93 ± 0.76
16	10.04 ± 0.86
17	10.53 ± 0.29
18	10.81 ± 1.13

From Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. *AJR Am J Roentgenol.* 1984;142:468.

Mean Renal Length: Spina Bifida

Age (yr)	Mean (cm)/SD
0.5	5.63 ± 0.42
1	6.26 ± 0.63
2	6.65 ± 0.55
3	6.97 ± 0.64
4	7.22 ± 0.66
5	7.63 ± 0.53
6	8.11 ± 0.52
7	8.14 ± 0.76
8	8.23 ± 0.76
9	8.95 ± 0.90
10	9.09 ± 0.73
11	9.34 ± 1.30
12	9.64 ± 0.90
13	9.83 ± 0.66
14	10.09 ± 1.10
15	9.71 ± 0.86
16	10.21 ± 0.93
17	10.04 ± 1.02
18	10.28 ± 1.13
≥19	10.23 ± 1.00

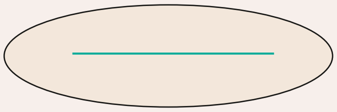
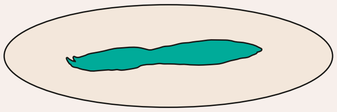
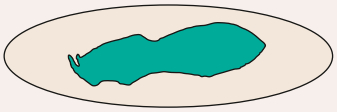
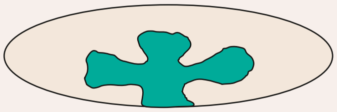
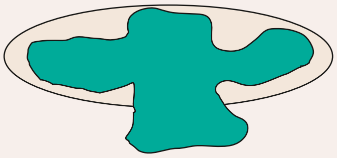
From Gross GW, Boal DK. Sonographic assessment of normal renal size in children with myelodysplasia. *J Urol.* 1988;140:784.

Grading Vesicoureteral Reflux

Grade I	Ureter only
Grade II	Ureter, pelvis, calyces, no dilation
Grade III	Mild or moderate dilation or tortuosity or both of the ureter; mild or moderate dilation of renal pelvis; slight blunting of the fornices
Grade IV	Moderate dilation or tortuosity or both of ureter and moderate dilation of renal pelvis and calyces; complete obliteration of sharp angle of fornices, but maintenance of papillary impression in most calyces
Grade V	Gross dilation and tortuosity of ureter; gross dilation of renal pelvis and calyces; papillary impressions are no longer visible in most calyces

From Report of the International Reflux Study Committee. Medical versus surgical treatment of primary vesicoureteral reflux. *Pediatrics.* 1981;67:392.

Ultrasound Grading of Hydronephrosis

Grade	Description	Image
0	Fat defines renal pelvis, no hydronephrosis, central renal complex intact	
1	Slight splitting of central renal complex	
2	Evident splitting of central renal complex, within renal border	
3	Wide splitting of central renal complex, pelvis dilated outside renal border, calyces uniformly dilated, normal renal parenchymal thickness	
4	Further dilation of pelvis and calyces; calyces may appear convex; thin renal parenchyma	

From Maizels M, Reisman ME, Flom S, et al. Grading nephroureteral dilatation detected in the first year of life: correlation with obstruction. *J Urol.* 1992;148:609-614.

Ultrasound Grading of Ureteral Dilation

Grade	Ureteral Diameter
1	<7 mm
2	7 ± 10 mm
3	>10 mm

From Maizels M, Reisman ME, Flom S, et al. Grading nephroureteral dilatation detected in the first year of life: correlation with obstruction. *J Urol.* 1992;148:609-614.

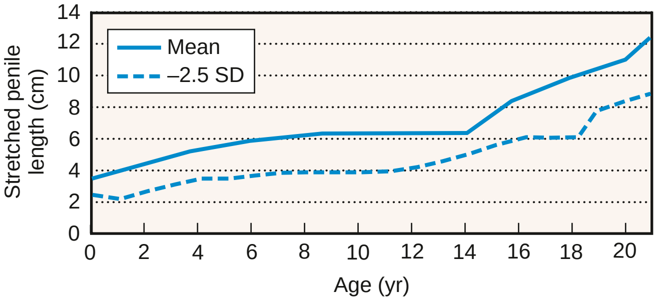
Tanner Stage: Male

Stage	Genitals	Pubic Hair
I	Testis, scrotum, penis equal to early childhood	None
II	Scrotum, testes enlarged; reddening of scrotal skin; texture of scrotal skin changes	Sparse, long, slightly pigmented, at base of penis
III	Penis grows first in length; further growth of testes, scrotum	Darker, coarser, more curled, spreads at junction of pubes
IV	Penis enlarges length and breadth; development of glans; testes, scrotum enlarge; darkening of scrotal skin	Adult quality, area covered smaller, no spread to medial thighs
V	Genitalia adult size and shape, no further enlargement	Adult quality, distribution inverse, triangular spread to medial thighs

From Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child.* 1970;45:13.

Penile Length

Based on Keefer JR. Endocrinology. In: Siberry GK, Iannone R, eds. *The Harriet Lane Handbook.* St. Louis: Mosby; 2000.



Tanner Stage: Female

Stage	Breast	Pubic Hair
I	Elevation of papilla	None
II	Elevation of breast bud, elevation of papilla, enlargement of areola (small mound)	Long, slightly pigmented, downy, straight, mainly on labia
III	Further development of breast and areola, no separation of their contours	Darker, coarse, more curled, spreads over pubes
IV	Projection of areola and papilla, forming a second mound above the breast	Hair quality adult, covers smaller area, no spread to medial thighs
V	Projection of papilla only, recession of areola, general smooth rounded contour of the breast	Hair quality adult, inverse triangle spreads to medial thighs

From Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44:291.

Testicular Size

Age (yr)	Tanner Stage	Volume (mL)	Length (cm)
1		1.4 ± 0.4	
2		1.4 ± 0.4	
4		1.5 ± 0.6	
6		1.8 ± 0.3	1
8	I	2 ± 0.5	2
10	II	2.7 ± 0.7	5
12	III	3.4 ± 0.8	10
14	IV	4.1 ± 1	20
16	V	5 ± 0.5	29
18		5 ± 0.5	29

Based on Keefer JR. Endocrinology. In: Siberry GK, Iannone R, eds. *The Harriet Lane Handbook.* St. Louis: Mosby; 2000.

EQUATIONS

Holliday-Segar Method: Fluids Maintenance*

Body Weight	Water	Electrolytes
First 10 kg	100 mL/kg/24 hr = 4 mL/kg/hr	Na^+ 3 mEq/100 mL H_2O
Second 10 kg	50 mL/kg/24 hr = 2 mg/kg/hr	Cl^- 2
Additional kg	20 mL/kg/24 hr = 1 mg/kg/hr	K^+ 2

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*>14 days of age.

From Choukair MK. Fluids and electrolytes. In: Siberry GK, Iannone R, eds. *The Harriet Lane Handbook*. St. Louis: Mosby; 2000.

Creatinine Clearance

Creatinine clearance = Ccr

C_{cr} (mL/min/1.73 m^2) = (U × V/P) × 1.73/BSA

U (mg/dL) = urinary creatinine concentration

V (mL/min) = total urine (mL) ÷ time collected (min)

P (mg/dL) = serum creatinine concentration

BSA (m^2) = body surface area

From Barratt TM, Auner ED, Harmon WE. *Pediatric Nephrology*. 4th Ed. Philadelphia: Lippincott Williams & Wilkins; 1999.

Glomerular Filtration Rate (GFR)

(Estimated) (GFR) = KL/P_{Cr} = mL/min/1.73 m^2

L = body length in cm

P_{Cr} = plasma creatinine

K = constant

K Values

Low-birth-weight infants: 0.33

Full-term infants: 0.45

Children: 0.55

Adolescent girls: 0.55

Adolescent boys: 0.7

From Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am.* 1987;34:571.

Normal Values of Glomerular Filtration Rate

	GLOMERULAR FILTRATION RATE	
Age	**Mean (mL/min/1.73 m^2)**	**Range (mL/min/1.73 m^2)**
Neonates <34 wk gestational Age		
2-8 days	11	11-15
4-28 days	20	15-28
30-90 days	50	40-65
Neonates >34 wk gestational Age		
2-8 days	39	17-60
4-28 days	47	26-68
30-90 days	58	30-86
1-6 mo	77	39-114
6-12 mo	103	49-157
12-19 mo	127	62-191
2 yr–adult	127	89-165

Bladder Capacity

Age + 2 = oz (× 30) = mL*

<2 yr 2 × age (yr) + 2 = oz (× 30) = mL†

>2 yr age (yr) ÷ 2 + 6 = oz (× 30) = mL†

---

*From Koff SA. Estimating bladder capacity in children. *Urology.* 1983;21:248.

†From Kaefer M, Zurakoski D, Bauer SB, et al. Estimating normal bladder capacity in children. *J Urol.* 1997;158:226.

LABORATORY REFERENCE INFORMATION

Reference Laboratory Values

The following reference information may vary depending on laboratory facilities. This information is used with permission from The 1997 Laboratory Handbook, Children's Health System, David R. Kelly, MD, Medical Director; Sherry R. Polhill, MBA, MT, Divisional Director. Published by Lexi Comp, Inc, Hudson, OH.

α-Fetoprotein

Synonyms: AFP

Reference Range: <8.5 ng/mL

Use: Germ cell neoplasms of the testis, ovary, retroperitoneum, mediastinum, hepatocellular carcinoma, monitor therapy of antineoplastic drugs

Additional Information: Elevated levels also present in nonmalignant hepatic disorders, viral hepatitis, chronic active hepatitis

Androstenedione

Reference Range: See the following table

Use: Evaluation of hirsutism or virilization, evaluation of androgen production and metabolism

Androstenedione, Serum

Age	Androstenedione, Serum (ng/dL)
Premature infants	80-466 (mean 207)
Full-term infants	
1-7 days	20-290 (mean 150); levels decrease rapidly to 18-80 ng/dL after 1 wk
1-12 mo	6-68 (mean 23); androstenedione gradually decreases during the first 6 mo to prepubertal levels
Prepubertal children (1-10 yr)	8-50 (mean 24)
Puberty	

	MALE		FEMALE	
Tanner Stage	Age (yr)	ng/dL	Age (yr)	ng/dL
I	<9.8	8-50 (mean 24)	<9.2	8-50 (mean 24)
II	9.8-14.5	31-65 (mean 45)	9.2-13.7	42-100 (mean 65)
III	10.7-15.4	50-100 (mean 67)	10-14.4	80-190 (mean 123)
IV	11.8-16.2	48-140 (mean 82)	10.7-15.6	77-225 (mean 131)
V	12.8-17.3	65-210 (mean 105)	11.8-18.6	80-240 (mean 160)
Adults (18-40 yr)		75-205 (mean 115)		Entire cycle: 85-275 (mean 165)

Cortisol, Serum or Urine

Synonyms: Cortisol, urinary free cortisol, urine cortisol

Reference Range: Urine: Infants to 10 yr, 2-27 µg/24 hr; 11-20 yr, 1-55 µg/24 hr. Serum: A.M. samples, 5-18 µg/dL; P.M. samples, 2-13 µg/dL

Use: Evaluation of suspected Cushing syndrome

Additional Information: Urinary cortisol reflects a portion of serum free cortisol filtered by the kidney; increase in adrenal cortical hyperfunction is helpful in differentiating Cushing syndrome from idiopathic obesity.

Creatinine, Blood

Reference Range: 0-2 yr, 0.2-0.6 mg/dL; 8 yr, 0.3-0.7 mg/dL; 11-13 yr, 0.4-0.8 mg/dL; 14-17 yr, 0.4-0.9 mg/dL; >16 yr, 0.7-1.5 mg/dL

Use: Renal function test

Additional Information: Oral ascorbic acid falsely elevates creatinine value.

Creatinine, Urine

Reference Range: 1.2-2 g/24 hr

Additional Information: Ascorbic acid falsely increases levels; increased with hypothyroidism, acromegaly, renovascular hypertension, and exercise; decreased with hyperthyroidism, progressive muscular dystrophy, myotonia atrophica, amyotrophic lateral sclerosis, and dermatomyositis/polymyositis.

Dehydroepiandrosterone Sulfate, Serum

Synonyms: DHEA sulfate; DHEA-S

Reference Range: See the following table

Use: Evaluation of adrenal deficiency or hirsutism or virilization (or both); elevated in congenital adrenal hyperplasia, adrenal cortical tumors; decreased in adrenal insufficiency, Cushing syndrome of pituitary origin, adrenal adenoma

Dehydroepiandrosterone Sulfate, Serum

Age	Male (µg/dL)	Female (µg/dL)
1-7 days	184-305	133-394
1-5 yr	0-36	0-57
6-10 yr	13-83	19-114
11-15 yr	32-305	32-229
16-20 yr	121-368	44-248

Deoxycorticosterone

Synonyms: DOC

Reference Range: See the following table

Deoxycorticosterone, Serum

Age	ng/dL
Cord blood	111-372 (mean 186)
Newborns	Levels markedly elevated at birth and decrease rapidly during first week to range found in older infants
Infants (1-12 mo)	7-49 (mean 23)
Prepubertal children (2-10 yr)	2-34 (mean 10.9)
Pubertal children and adults, 8 A.M.	2-19 (mean 7.1)

Dihydrotestosterone

Synonyms: DHT, dihydrotestosterone sulfate

Reference Range: Male, 30-85 ng/dL; female, 8-28 ng/dL

Use: Evaluation of male hypogonadism

Additional Information: Testosterone is converted to DHT intracellularly in the target tissue. There is very little leakage of DHT back into the circulation. Plasma DHT is not now considered to be of significant diagnostic usefulness.

Estradiol, Serum

Synonyms: Estradiol (E_2)

Reference Range: See the following table

Use: Assessment of hypothalamic and pituitary function

Additional Information: In males, estradiol level is low or normal in hypopituitarism, Kallmann's syndrome, isolated gonadotropic deficiency, primary testicular failure, and anorchia. It is normal in cryptorchidism, azoospermia, and oligospermia. It is normal or increased in Klinefelter's syndrome and in precocious puberty related to adrenal tumors or congenital adrenal hyperplasia. It is increased in precocious puberty related to idiopathic or central nervous system lesions and complete testicular feminization.

Estradiol, Serum

Age	ng/dL	
Cord blood	300-2900 (mean 810)	
Newborns (1-7 days)	Estradiol levels markedly elevated at birth and decrease rapidly during the first week to prepubertal values	
1-6 mo	*Male*	*Female*
	Levels increase to 1-3.2 ng/dL between 30-60 days, then decline to <1.5 ng/dL by 6 mo	Levels increase to 0.5-5 ng/dL between 30-60 days, then decline to <1.5 ng/dL during first year
Prepubertal children (1-10 yr)	<1.5	
Puberty		

	MALE		FEMALE	
Tanner Stage	**Age (yr)**	**ng/dL**	**Age (yr)**	**ng/dL**
I	<9.8	0.5-1.1 (mean 0.8)	<9.2	0.1-2 (mean 0.8)
II	9.8-14.5	0.5-1.6 (mean 1.1)	9.2-13.7	1-2.4 (mean 1.6)
III	10.7-15.4	0.5-2.5 (mean 1.6)	10-14.4	0.7-6 (mean 2.5)
IV	11.8-16.2	1-3.6 (mean 2.2)	10.7-15.6	2.1-8.5 (mean 4.7)
V	12.8-17.3	1-3.6 (mean 2.1)	11.8-18.6	3.4-17 (mean 11)
Adults		0.8-3.5 (mean 2)		Follicular: 3-10 (mean 5.2) Luteal: 7-30 (mean 13)

Estrogens, Serum

Reference Range: See the following table

Use: Evaluation of ovarian estrogen-producing tumors, evaluation of estrogen excess in males

Estrogens, Serum

Age	ng/dL
Cord blood	750-6500 (mean 2430)
Full-term infants (1-7 days)	Estrogens markedly elevated at birth and decrease rapidly during first week to reach prepubertal levels by 7 days
1-6 mo	Levels increase in early infancy to a range of 1-4 ng/dL in males and 1-6 ng/dL in females between 30-60 days
Prepubertal children (1-10 yr)	<2.5
Puberty	

	MALE		FEMALE	
Tanner Stage	Age (yr)	ng/dL	Age (yr)	ng/dL
I	<9.8	1-3.8 (mean 2)	<9.2	1-4.6 (mean 2.3)
II	9.8-14.5	1.7-4.5 (mean 3)	9.2-13.7	2.2-6.3 (mean 4.1)
III	10.7-15.4	2.2-5.5 (mean 4.1)	10-14.4	2.4-11 (mean 6.1)
IV	11.8-16.2	2.7-8 (mean 5.3)	10.7-15.6	4-18 (mean 9.1)
V	12.8-17.3	2.5-8 (mean 5)	11.8-18.6	6-28 (mean 17)
Adults		2-8 (mean 5.9)		Follicular: 6-20 (mean 13) Luteal: 16-40 (mean 26)

Follicle-Stimulating Hormone

Synonyms: FSH

Reference Range: See the following table

Use: Evaluation of neuroendocrine gonadal function

Additional Information: Low or normal in hyperpituitarism, Kallmann's syndrome, isolated gonadotropin deficiency, delayed puberty, and Stein-Leventhal syndrome. Normal or increased in cryptorchidism, azoospermia and oligospermia, and complete testicular feminization. High in primary testicular failure, anorchia, Klinefelter's syndrome, Turner syndrome, and idiopathic or central nervous system lesions causing precocious puberty. Low in precocious puberty related to adrenal tumors or congenital adrenal hyperplasia.

Follicle-Stimulating Hormone, Blood

Age	mIU/mL	
Cord blood	<1	
Newborns (1-7 days)	<1-2.4 (mean 1.1)	
2 wk–2 yr	*Male*	*Female*
	Levels increase about 2 wk after birth to <1-20 mIU/mL, then decline to prepubertal levels within the first year	Levels increase about 2 wk after birth to <1-31 mIU/mL, then decline gradually to prepubertal levels after 2 yr. FSH levels in females exhibit less relationship with age, but are significantly higher than in males
Prepubertal children	<1-3.2 (mean 2.1)	<1-5 (mean 3.5)
Puberty		

	MALE		FEMALE	
Tanner Stage	Age (yr)	ng/dL	Age (yr)	ng/dL
I	<9.8	<1-3 (mean 2.1)	<9.2	<1-3 (mean 2.1)
II	9.8-14.5	2-7 (mean 3.4)	9.2-13.7	<1-6 (mean 3.4)
III	10.7-15.4	2-8 (mean 4.8)	10-14.4	1.5-9 (mean 5)
IV	11.8-16.2	2-8 (mean 6)	10.7-15.6	2-9 (mean 6.1)
V	12.8-17.3	1-8 (mean 5.9)	11.8-18.6	1-9 (mean 5.9)
Adults		1-8 (mean 4.7)		Follicular: 1-9 (mean 5.5)
				Midcycle: 4-30
				Luteal: <1.7 (mean 5.1)

FSH, follicle-stimulating hormone.

Growth Hormone

Synonyms: Arginine stimulation; HGH; human growth hormone; levodopa stimulation

Reference Range: Children (overnight fast), <16 ng/mL; newborns, <140 ng/mL

Additional Information: Marked fluctuations in HGH concentration occur in normal individuals; random sampling does not give useful information

Human Chorionic Gonadotropin, Beta Subunit

Synonyms: Beta subunit, hCG; quantitative beta subunit hCG

Reference Range: Nonpregnant, <10 mIU/mL; indeterminate, 10-20 mIU/mL; pregnant, first trimester, 10,000-160,000 mIU/mL; second trimester, 6000-30,000 mIU/mL; third trimester, 4000-15,000 mIU/mL; postpartum, <10 mIU/mL

Use: Detection of early pregnancy, ectopic pregnancy, or a threatened abortion. Elevated levels are found in choriocarcinoma and embryonal cell carcinoma.

Additional Information: Various poorly differentiated or undifferentiated neoplasms produce ectopic chorionic gonadotropin, including choriocarcinoma, hydatidiform mole, and germinal testicular tumors.

17-Hydroxycorticosteroids, Urine

Synonyms: 17-OHCS

Reference Range: Male, 3-12 mg/24 hr; female, 2-8 mg/24 hr

Use: Evaluation of glucocorticoid production

17-Hydroxypregnenolone

Synonyms: 17-OH Preg

Reference Range: See the following table

Use: Evaluation of adrenal function, especially 17-desmolase deficiency in congenital adrenal hyperplasia

17-Hydroxypregnenolone

Age	ng/dL
Cord blood	50-2121
Premature infants	64-2380
Full-term infants	
3 days	10-829
1-6 mo	36-763
6-12 mo	42-540
Prepubertal children (1-10 yr)	15-221
Pubertal age groups	44-235
Adults	53-357

17-Hydroxyprogesterone

Synonyms: 17-OHP

Reference Range: See the following table

Use: Assess congenital adrenal hyperplasia caused by inadequate levels of 21-hydroxylase or 11-β-hydroxysteroid dehydrogenase or both

17-Hydroxyprogesterone

Age	ng/dL	
Cord blood	900-5000 (mean 1900)	
Premature infants	26-568 (mean 248)	
Full-term infants (3 days)	7-77 (mean 36)	
1-12 mo	*Male*	*Female*
	Levels increase after the first week to peak values 40-200 ng/dL between 30-60 days. Values then decline to prepubertal range before 1 yr	13-106 (mean 31)
Prepubertal children (1-10 yr)	3-90 (mean 38)	
Puberty		

	Male		Female	
Tanner Stage	**Age (yr)**	**ng/dL**	**Age (yr)**	**ng/dL**
I	<9.8	3-90 (mean 38)	<9.2	3-82 (mean 31)
II	9.8-14.5	5-115 (mean 51)	9.2-13.7	11-98 (mean 49)
III	10.7-15.4	10-138 (mean 57)	10-14.4	11-155 (mean 70)
IV	11.8-16.2	29-180 (mean 80)	10.7-15.6	18-230 (mean 91)
V	12.8-17.3	24-175 (mean 97)	11.8-18.6	20-265 (mean 108)
Adults		27-199 (mean 103)		Follicular: 15-70 (mean 46) Luteal: 35-290 (mean 165)

17-Ketogenic Steroids, Total

Synonyms: 17-KS

Reference Range: Male, 5-23 mg/24 hr; female, 3-15 mg/24 hr

Use: Evaluation of adrenogenital syndrome; virilization, Cushing syndrome

17-Ketosteroids, Total, Urine

Synonyms: 17-KS

Reference Range: See the following table

17-Ketosteroids (17-KS)

Age (yr)	mg/24 hr	mg/g Creatinine
Children		
1-4	<1-2	
5-9	<1-3.2 (mean 1.6)	
10-12	1-5 (mean 2.4)	
12-14	1-5.5 (mean 3.1)	Not determined
Male (15-25)	3-13 (mean 6.6)	
Female (15-25)	2.5-8 (mean 3.5)	
Adults		
Male	10-25 (mean 15.6)	6.7-12 (mean 9.5)
Female	6-14 (mean 9.4)	5.6 (mean 7.8)

Luteinizing Hormone, Serum

Synonyms: ICSH; interstitial cell stimulating hormone; LH

Reference Range: See the following table

Use: Defining the hypothalamic-pituitary-gonadal axis. Distinguishes between primary gonadal failure and deficient gonadal stimulation

Additional Information: Males low or normal in hypopituitarism, Kallmann's syndrome, isolated gonadotropin deficiency, and delayed puberty. Normal in cryptorchidism. Normal or high in azoospermia, oligospermia, and Klinefelter's syndrome. High with complete testicular feminization, and precocious puberty related to central nervous system lesion. Low in precocious puberty related to adrenal tumors or congenital adrenal hyperplasia.

Luteinizing Hormones, Serum

Age	mIU/mL	
Newborns (1 wk)	1.5-3 (mean 22)	
2 wk–1 yr	*Male*	*Female*
	Values begin to increase about 2 wk after birth to 3.5-25 mIU/mL in 1-3 mo, then decline to prepubertal values by end of first year	Values increase within the first 2 mo to 2.1-14 mIU/mL, then decline to prepubertal levels by end of first year
Prepubertal children	<1-4 (mean 2.4)	
Puberty		

	Male		Female	
Tanner Stage	**Age (yr)**	**ng/dL**	**Age (yr)**	**ng/dL**
I	<9.8	<1-4 (mean 2.4)	<9.2	<1-4 (mean 2.4)
II	9.8-14.5	<1-5 (mean 3.5)	9.2-13.7	<1-5 (mean 3)
III	10.7-15.4	2-10 (mean 4)	10-14.4	<1-10 (mean 5.9)
IV	11.8-16.2	2-10 (mean 4.8)	10.7-15.6	3-11 (mean 6.3)
V	12.8-17.3	4.5-11 (mean 6.4)	11.8-18.6	2-12 (mean 6.1)
Adults		3-10 (mean 5.2)		Follicular: 3-11 (mean 5.9)
				Midcycle: 18-70
				Luteal: 2-11 (mean 5.3)

Pregnenolone

Reference Range: See the following table

Use: Evaluation of adrenal function, particularly in 17-hydroxylase deficiency in congenital adrenal hyperplasia

Pregnenolone

Age	ng/dL
Newborns (1-7 days)	150-2000 (mean 650); levels decrease after birth and are within prepubertal range by 3 mo
Infants and prepubertal children	20-110 (mean 54)
Pubertal age groups (11-16 yr)	50-126 (mean 93)
Adults	46-225 (mean 111)

Progesterone, Serum

Reference Range: See the following table

Use: Evaluation of ovarian function

Additional Information: Increased in choriocarcinomas, ovarian Sertoli-Leydig cell tumors, adrenal cortical hyperfunction, ovarial (luteal) cysts, hydatidiform mole, and pregnancy

Progesterone, Serum

Age	ng/dL
Premature infants	84-1360 (mean 347)
Full-term infants (1-7 days)	Progesterone levels markedly elevated in neonates, but decrease rapidly to reach prepubertal levels by 7 days and remain steady until puberty
Prepubertal children (1-10 yr)	7-52 (mean 29)
Puberty	

	Male		Female	
Tanner Stage	**Age (yr)**	**ng/dL**	**Age (yr)**	**ng/dL**
I	<9.8	<10-33 (mean 22)	<9.2	<10-33 (mean 22)
II	9.8-14.5	<10-33 (mean 22)	9.2-13.7	<10-55 (mean 32)
III	10.7-15.4	<10-48 (mean 26)	10-14.4	10-450 (mean 37)
IV	11.8-16.2	10-108 (mean 36)	10.7-15.6	10-1300 (mean 290)
V	12.8-17.3	21-82 (mean 39)	11.8-18.6	10-950 (mean 160)
Adults		13-97 (mean 33)		Follicular: 15-70 (mean 32)
				Luteal: 200-2500 (mean 750)

Testosterone, Free

Reference Range: See the following table

Use: Evaluation of hirsutism and masculinization in females; evaluation of testicular function

Additional Information: Free testosterone is usually increased in hirsute women.

Testosterone, Free

	Male		Female	
Age	**% Free**	**pg/mL**	**% Free**	**pg/mL**
Infants				
1-15 days	0.9-1.7	1.5-31	0.8-1.5	0.5-2.5
1-3 mo	0.4-0.8	3.3-18	0.4-1.1	0.1-0.3
3-5 mo	0.4-1.1	0.7-14	0.5-1	0.2-1.1
5-7 mo	0.4-1	0.4-4.8	0.5-0.8	0.2-0.6
Prepubertal children	0.4-0.9	0.15-0.6	0.4-0.9	0.15-0.6
Adults	1.5-3.2	52-280	0.8-1.4	1.1-6.3

Testosterone, Serum

Reference Range: See the following table

Use: A reliable indicator of luteinizing hormone secretion and Leydig cell function; evaluation of gonadal and adrenal function; diagnosis of hypogonadism in males and hirsutism and virilization in females

Additional Information: Testosterone level is normal or decreased in hypopituitarism, Kallmann's syndrome, isolated gonadotropin deficiency, and Klinefelter's syndrome. Normal in cryptorchidism, azoospermia, and oligospermia. Decreased in delayed puberty, primary testicular failure, and anorchia. Normal or increased in testicular feminization. Increased in precocious puberty related to idiopathic or central nervous system lesions, adrenal tumors, or congenital adrenal hyperplasia.

Testosterone, Serum

Age	Male (ng/dL)	Female (ng/dL)
Premature infants	37-198 (mean 126)	5-22 (mean 12)
Full-term newborns	75-400 (mean 200)	20-64 (mean 39)
1-7 mo	Levels decrease rapidly the first week to 20-50 ng/dL, then increase to 60-400 ng/dL (mean 190) between 20-60 days. Levels then decline to prepubertal range by 7 mo	Levels decrease during the first month to <10 ng/dL and remain there until puberty
Prepubertal children (1-10 yr)	<3-10 (mean 4.9)	
Puberty		

	Male		Female	
Tanner Stage	**Age (yr)**	**ng/dL**	**Age (yr)**	**ng/dL**
I	<9.8	<3-10 (mean 4.9)	<9.2	<3-10 (mean 4.9)
II	9.8-14.5	18-150 (mean 42)	9.2-13.7	7-28 (mean 18)
III	10.7-15.4	100-320 (mean 190)	10-14.4	15-35 (mean 25)
IV	11.8-16.2	200-620 (mean 372)	10.7-15.6	13-32 (mean 22)
V	12.8-17.3	350-970 (mean 546)	11.8-18.6	20-38 (mean 28)
Adults		350-1030 (mean 627)		10-55 (mean 32)

Urea Nitrogen, Blood

Synonyms: BUN

Reference Range: 4-18 mg/dL

Use: Diagnosis of azotemia and uremia

Additional Information: Increased in chronic glomerulonephritis, pyelonephritis, and renal disease

Vanillylmandelic Acid, Quantitative, Urine

Synonyms: VMA

Reference Range: 2-7 mg/24 hr

Additional Information: Increased levels in neuroblastoma, pheochromocytoma, and malignant hypertension

Substances That May Color the Urine

Color	Pathologic	Nonpathologic
White	Bacteria	Phosphates
	Chyle	Urates
	Pus	
Colorless to pale yellow	Chronic nephritis	Decreased normal pigment
	Diabetes	Dilute urine
	Diuresis	
Yellow to amber	Bilirubin	Normal pigments
	Urobilin	
Orange		Acriflavine
		Azo Gantrisin
		Carrots or vitamin A
		Food color
		Nitrofurantoin
		Pyridium
		Serotonin
		Sulfasalazine
Pink to red	Hemoglobin	Aminopyrine
	Myoglobin	Antipyrine
	Porphobilin	Beets (anthocyanin)
	Porphyrins	Bromosulfophthalein
	Red blood cells	Cascara
		Phenytoin
		Food color
		Methyldopa
		Phenacetin
		Phenolphthalein
		Phenolsulfophthalein
		Phenothiazine
		Pyridium
		Senna
Port wine	Porphobilin	
	Porphobilinogen	
	Uroporphyrin	
Brown to black	Bilirubin	Chloroquine
	Homogentisic acid	Hydroquinone
	Indican	Iron compounds
	Melanin	Levodopa
	Methemoglobin	Methyldopa
	Myoglobin	Metronidazole
	p-Hydroxyphenylpyruvic acid	Nitrofurantoin
	Phenol	Quinine
	Porphyrins	Resorcinol
Blue to green	Biliverdin	Acriflavine
	Pseudomonas infection	Amitriptyline
		Azure A
		Creosote
		Evans blue
		Indigo pigment
		Methylene blue
		Phenylsalicylate
		Thymol
		Tolonium
		Triamterene
		Vitamin B complex

FORMULARY

Generic Name: Acetaminophen
Trade Name: Tylenol, Tempra, Panadol, Feverall
Drug Class: Analgesic, antipyretic
Use: Control of fever and pain
Cautions: Renal
Dosing: Pediatric: 10-15 mg/kg/dose q 4-6 hr PO/PR
Forms: Infant drops: 80 mg/0.8 mL
Children's solution/suspension: 160 mg/5 mL
Elixir: 80, 120, 160, 325 mg/5 mL
Sprinkle capsules: 80, 160 mg
Suppositories: 80, 120, 125, 325, 650 mg
Chewable tabs: 80, 160 mg; tabs: 160, 325, 500, 650 mg

Generic Name: Amikacin sulfate
Trade Name: Amikin (Amiklin [France]; Amikin [UK])
Drug Class: Aminoglycoside
Use: Antibiotic
Cautions: Renal, pregnancy
Dosing: Infants and children: 15-22.5 mg/kg/24 hr ÷ q 8 hr IV/IM
Initial maximum dose: 1.5 g/24 hr
Therapeutic levels: peak 20-30 mg/L; trough 5-10 mg/L
Neonates: 30-36 wk gestational age: 10 mg/kg/dose q 24 hr
Neonates: >37 wk gestational age, <7 days: 7.5 mg/kg/dose q 12 hr
Neonates: >7 days: 7.5 mg/kg/dose q 8 hr

Generic Name: Amoxicillin
Trade Name: Amoxil, Trimox, Wymox, Polymox (A-Gram, Amodex [France]; Amoxil, Almodon [UK])
Drug Class: Aminopenicillins
Use: Antibiotic
Cautions: Renal
Dosing: 20-50 mg/kg/24 hr ÷ tid PO
Forms: Drops: 50 mg/kg/mL
Suspension: 125, 250 mg/5 mL
Caps: 250, 500 mg
Chewable tabs: 125, 250 mg

Generic Name: Amoxicillin-clavulanic acid
Trade Name: Augmentin (Augmentin [France]; Augmentin [UK])
Drug Class: Aminopenicillins, β-lactamase inhibitor
Use: Antibiotic
Cautions: Renal
Dosing: <3 mo: 30 mg/kg/24 hr ÷ bid PO
>3 mo: 20-40 mg/kg/24 hr ÷ tid PO
Forms: Tabs: 250, 500 mg (with 125 mg clavulanate)
Chewable tabs: 125, 250 mg amoxicillin (31.25 and 62.5 mg clavulanate)
Suspension: tid dose 125, 250 mg amoxicillin/5 mL (31.25 and 62.5 mg clavulanate)
Suspension: bid dose 200, 400 mg amoxicillin/5 mL (28.5 and 57 mg clavulanate)

Generic Name: Amphotericin B
Trade Name: Fungizone, Amphocin (Fungizone [France]; Abelcet, Ambisome, Fungizone [UK])
Drug Class: Antifungal
Use: Intravesical irrigation
Dosing: 50 mg amphotericin B in 1 L sterile water for urinary irrigation only

Generic Name: Ampicillin
Trade Name: Omnipen, Polycillin, Principen, Totacillin (Penicline, Prototapen, Totapen [France]; Amfipen, Flu-Amp, Rimacillin [UK])
Drug Class: Aminopenicillins
Use: Antibiotic
Dosing: Neonates: <7 days and <2 kg: 50-100 mg/kg/24 hr ÷ q 12 hr IM/IV
Neonates: <7 days and >2 kg: 75-150 mg/kg/24 hr ÷ q 8 hr IM/IV
Neonates: >7 days >2 kg: 100-200 mg/kg/24 hr ÷ q 6 hr IM/IV
Children: 100-200 mg/kg/24 hr ÷ q 6 (maximum dose 2-3 g/24 hr) PO
Forms: Drops: 100 mg/mL
Suspension: 125, 250, 500 mg/5 mL
Caps: 250, 500 mg
Injection: 125, 250, 500 mg; 1, 2, 10 g

Generic Name: Azithromycin
Trade Name: Zithromax (Azadose, Zithromax [France]; Zithromax [UK])
Drug Class: Macrolide
Use: Antibiotic
Dosing: >6 mo: 10 mg/kg qd (day 1) followed by 5 mg/kg/24 hr qd PO
>2 yr: 12 mg/kg/24 hr qd PO
Adolescents with uncomplicated chlamydial urethritis or cervicitis: single 1 g-dose PO
Acute pelvic inflammatory disease (*Chlamydia*): 500 mg IV qd × 1-2 days followed by 250 mg qd PO
Forms: Tablets: 250, 600 mg
Capsules: 250 mg
Suspension: 100, 200 mg/5 mL
Oral powder (sachet): 1 g

Generic Name: Aztreonam
Trade Name: Azactam (Azactam [France]; Azactam [UK])
Drug Class: Monobactam
Use: Antibiotic
Cautions: Renal
Dosing: Neonates: >2 kg and >7 days: 30 mg/kg/dose q 6 hr
Children: 90-100 mg/kg/24 hr ÷ q 6/8 hr

Generic Name: Bethanechol chloride
Trade Name: Urecholine (Myotonine [UK])
Drug Class: Cholinergic
Use: Urinary retention
Dosing: 0.6 mg/kg/24 hr ÷ q 6-8 hr PO
Forms: Tabs: 5, 10, 25, 50 mg
Suspension: 1 mg/mL

Generic Name: Bisacodyl
Trade Name: Dulcolax
Drug Class: Cathartic
Use: Constipation
Dosing: 3-12 yr: 0.3 mg/kg/24 hr (5 or 10 mg) PO
<2 yr: 5 mg/24 hr PR
2-11 yr: 5-10 mg/24 hr PR
Forms: Suppository: 5, 10 mg
Tabs (enteric coated): 5 mg

Generic Name: Bupivacaine
Trade Name: Marcaine, Sensorcaine (Marcaine [France]; Marcain [UK])
Drug Class: Local anesthetic
Use: Analgesia
Dosing: 2.5 mg/kg maximum; 3 mg/kg (with epinephrine 1:200,000) maximum
Forms: 0.25%, 0.5%, 0.75% ± epinephrine

Generic Name: Captopril
Trade Name: Capoten (Captirex, Captolane [France] Acepril, Capoten, Ecopace [UK])
Drug Class: Angiotensin-converting enzyme inhibitor
Use: Antihypertensive
Cautions: Renal
Dosing: Neonates: 0.1-0.4 mg/kg/24 hr PO ÷ q 6-8 hr
Infants: 0.15-0.3 mg/kg/dose, maximum dose 6 mg/kg/24 hr ÷ qd-qid
Children: 0.3-0.5 mg/kg/dose q 8 hr, maximum dose 6 mg/kg/24 hr ÷ bid-qid
Adolescents: 12.5-25 mg/dose PO bid-tid, maximum dose 400 mg/24 hr
Forms: Tabs: 12.5, 25, 50, 100 mg
Suspension: 0.75, 1 mg/mL

Generic Name: Carbenicillin
Trade Name: Geocillin, Geopen, Pyopen (Pyopen [UK])
Drug Class: Penicillin
Use: Antibiotic
Cautions: Renal
Dosing: Children: 30-50 mg/kg/24 hr ÷ q 6 hr PO
Forms: Tabs: 382 mg

Generic Name: Cefaclor
Trade Name: Ceclor (Alfatil [France]; Distaclor, Keftio [UK])
Drug Class: Cephalosporin (second generation)
Use: Antibiotic
Cautions: Renal
Dosing: 20-40 mg/kg/24 hr ÷ q 8 hr PO
Forms: Capsule: 25, 50 mg
Extended-release tabs: 375, 500 mg
Suspension: 125, 187, 250, 375 mg/5 mL

Generic Name: Cefadroxil
Trade Name: Duricef, Ultracef (Oracefal [France]; Boxan [UK])
Drug Class: Cephalosporin (first generation)
Use: Antibiotic
Cautions: Renal
Dosing: 30 mg/kg/24 hr PO ÷ q 12 hr PO
Forms: Suspension: 125, 250, 500 mg/5 mL
Tabs: 1 g
Caps: 500 mg

Generic Name: Cefamandole
Trade Name: Mandol (Kefandol [France]; Kefadol [UK])
Drug Class: Cephalosporin (second generation)
Use: Antibiotic
Cautions: Renal
Dosing: 50-150 mg/kg 24 hr IM/IV ÷ q 4-6 hr IV/IM
Forms: Injection: 0.5, 1, 2, 10 g

Generic Name: Cefazolin
Trade Name: Ancef, Kefzol, Zolicef
Drug Class: Cephalosporin (first generation)
Use: Antibiotic
Cautions: Renal
Dosing: >7 days and >2000 g: 60 mg/kg/24 hr ÷ q 8 hr IV/IM
>1 month: 50-100 mg/kg/24 hr ÷ q 8 hr IV/IM
Forms: Injection: 0.25, 0.5, 1, 5, 10, 20 g

Generic Name: Cefdinir
Trade Name: Omnicef
Drug Class: Cephalosporin (third generation)
Use: Antibiotic
Cautions: Renal
Dosing: 6 mo-12 yr: 14 mg/kg/24 hr PO ÷ q 12 hr, maximum dose 600 mg/24 hr
≥13 yr: 600 mg/24 hr PO ÷ q 12 hr
Forms: Capsules: 300 mg
Suspension: 125 mg/5 mL

Generic Name: Cefepime
Trade Name: Maxipime (Axepim [France])
Drug Class: Cephalosporin (fourth generation)
Use: Antibiotic
Cautions: Renal
Dosing: >2 mo: 100 mg/kg/24 hr ÷ q 12 hr IV/IM
Forms: Injection: 0.5, 1, 2 g

Generic Name: Cefixime
Trade Name: Suprax (Oroken [France]; Suprax [UK])
Drug Class: Cephalosporin (third generation)
Use: Antibiotic
Cautions: Renal
Dosing: Infants and children: 8 mg/kg/24 hr ÷ q 12-24 hr PO
Adolescent: 400 mg/24 hr ÷ q 12 hr PO
Cervical, urethral, rectal *Neisseria gonorrhoeae*: 400 mg × 1 PO
Forms: Tabs: 200, 400 mg
Suspension: 100 mg/5 mL

Generic Name: Cefoperazone
Trade Name: Cefobid (Cefobis [France])
Drug Class: Cephalosporin (third generation)
Use: Antibiotic
Dosing: 100-200 mg/kg/24 hr ÷ q 8-12 hr IV/IM
Forms: Injection: 1, 2, 10 g

Generic Name: Cefotaxime
Trade Name: Claforan (Claforan [France]; Claforan [UK])
Drug Class: Cephalosporin (third generation)
Use: Antibiotic
Cautions: Renal
Dosing: >7 days and >1200 g: 150 mg/kg/24 hr ÷ q 8 hr IV/IM
Children <50 kg: 100-200 mg/kg/24 hr ÷ q 6-8 hr IV/IM
Forms: Injection: 0.5, 1, 2, 10 g

Generic Name: Cefotetan
Trade Name: Cefotan (Apacef [France])
Drug Class: Cephalosporin (second generation)
Use: Antibiotic
Cautions: Renal
Dosing: 40-80 mg/kg/24 hr ÷ q 12 hr IV/IM
Forms: Injection: 1, 2, 10 g

Generic Name: Cefoxitin
Trade Name: Mefoxin (Mefoxin [France]; Mefoxin [UK])
Drug Class: Cephalosporin (second generation)
Use: Antibiotic
Cautions: Renal
Dosing: 80-160 mg/kg/24 hr ÷ q 4-8 hr IM/IV
Forms: Injection: 1, 2, 10 g

Generic Name: Cefpodoxime proxetil
Trade Name: Vantin (Cefodox [France]; Orelox [UK])
Drug Class: Cephalosporin (second generation)
Use: Antibiotic
Cautions: Renal
Dosing: <12 yr: 10 mg/kg/24 hr ÷ q 12-24 hr PO
>13 yr: 200-800 mg/kg/24 hr ÷ q 12 hr PO
Uncomplicated gonorrhea: 200 mg × 1 PO
Forms: Tabs: 100, 200 mg
Suspension: 50, 100 mg/5 mL

Generic Name: Cefprozil
Trade Name: Cefzil (Cefzil [UK])
Drug Class: Cephalosporin (second generation)
Use: Antibiotic
Cautions: Renal
Dosing: <12 yr: 30 mg/kg/24 hr ÷ q 12 hr PO
>12 yr: 500-1000 mg/kg/24 hr ÷ q 12-24 hr PO
Forms: Tabs: 250, 500 mg
Suspension: 125, 250 mg/5 mL

Generic Name: Ceftazidime
Trade Name: Fortaz, Tazidime, Tazicef, Ceptaz (Fortum [France]; Fortum, Kefadim [UK])
Drug Class: Cephalosporin (third generation)
Use: Antibiotics
Cautions: Renal
Dosing: >7 days and >1200 g: 150 mg/kg/24 hr ÷ q 8 hr IV/IM
Children: 90-150 mg/kg/24 hr ÷ q 8 hr IV/IM
Forms: Injection: 0.5, 1, 2, 6, 10 g

Generic Name: Ceftibuten
Trade Name: Cedax (Cedax [UK])
Drug Class: Cephalosporin (third generation)
Use: Antibiotic
Cautions: Renal
Dosing: Children: 9 mg/kg/24 hr PO qd
>12 yr: 400 mg hr PO qd
Forms: Suspension: 90, 180 mg/5 mL
Tabs: 400 mg

Generic Name: Ceftriaxone
Trade Name: Rocephin (Rocephine [France]; Rocephin [UK])
Drug Class: Cephalosporin (third generation)
Use: Antibiotic
Dosing: 50-75 mg/kg/24 hr ÷ q 12-24 hr IM/IV
Forms: Injection: 0.25, 0.5, 1, 2, 10 g

Generic Name: Cefuroxime
Trade Name: IV: Zinacef, Kefurox; PO: Ceftin (Cepazine, Zinnat [France]; Zinacef, Zinnat [UK])
Drug Class: Cephalosporin (second generation)
Use: Antibiotic
Cautions: Renal
Dosing: Neonates: 30 mg/kg/24 hr ÷ q 12 hr PO
Children: 75-150 mg/kg/24 hr ÷ q 8 hr IM/IV
Forms: 0.75, 1.5, 7.5 g IV/IM
Tabs: 125, 250, 500 mg
Suspension: 125, 250 mg/5 mL

Generic Name: Cephalexin
Trade Name: Keflex, Cefanex, C-Lexin (Cefacet, Ceporexine, Keforal [France]; Ceporex, Keflex, Kiflone [UK])
Drug Class: Cephalosporin (first generation)
Use: Antibiotics
Cautions: Renal
Dosing: 25-100 mg/kg/24 hr ÷ q 6 hr PO
Forms: Tabs: 250, 500 mg, 1 g
Caps: 250, 500 mg
Suspension: 125, 250 mg/5 mL
Drops: 100 mg/mL

Generic Name: Cephalothin
Drug Class: Cephalosporin (first generation)
Use: Antibiotic
Cautions: Renal
Dosing: Neonates: >7 days and >2 kg: 80 mg/kg/24 hr ÷ q 6 hr IV/IM
Children: 80-160 mg/kg/24 hr ÷ q 4-6 hr IV/IM
Forms: Injection: 1, 2 g

Generic Name: Cephradine
Trade Name: Velosef (Doncef, Kelsef, Zadyl [France]; Nicef, Velosef [UK])
Drug Class: Cephalosporin (first generation)
Use: Antibiotic
Cautions: Renal
Dosing: 25-50 mg/kg/24 hr ÷ q 6-12 hr PO
Forms: Suspension: 125, 250 mg/5 mL
Caps: 250, 500 mg
Injection: 0.25, 0.5, 1, 2 g

Generic Name: Cetirizine
Trade Name: Zyrtec (Virlix, Zyrtec [France]; Zirtek [UK])
Drug Class: Antihistamine
Use: Allergy, hives
Cautions: Renal
Dosing: 2-5 yr: 2.5 mg PO qd
>6 yr: 5-10 mg PO qd
Forms: Syrup: 5 mg/5 mL
Tabs: 5, 10 g

Generic Name: Chloral hydrate
Trade Name: Noctec, Aquachloral Supprettes (Noctec, Welldorm [UK])
Drug Class: Hypnotic
Use: Sedative
Cautions: Renal
Dosing: 25-100 mg/kg/dose PO/PR
Forms: Caps: 250, 500 mg
Syrup: 250, 500 mg
Suppository: 324, 500, 648 mg

Generic Name: Chlorothiazide
Trade Name: Diuril, Diurigen (Salvric [UK])
Drug Class: Thiazide diuretic
Use: Diuretic
Cautions: Renal
Dosing: >6 mo: 20-40 mg/kg/24 hr ÷ q 12 hr PO
Forms: Tabs: 250, 500 mg
Suspension: 250 mg/5 mL
Injection: 500 mg

Generic Name: Cimetidine
Trade Name: Tagamet
Drug Class: Histamine-2 antagonist
Cautions: Renal
Dosing: Neonates: 5-20 mg/kg/24 hr ÷ q 6-12 hr PO/IV/IM
Infants: 10-20 mg/kg/24 hr ÷ q 6-12 hr PO/IV/IM
Children: 20-40 mg/kg/24 hr ÷ q 6 hr PO/IV/IM
Forms: Syrup: 300 mg/5 mL
Tabs: 200, 300, 400, 800 mg

Generic Name: Ciprofloxacin
Trade Name: Cipro (Ciflox, Uniflox [France]; Ciloxan, Ciproxin [UK])
Drug Class: Quinolone
Use: Antibiotic
Cautions: Renal (not approved for children)
Dosing: 20-30 mg/kg/24 hr ÷ q 12 hr PO
10-20 mg/kg/24 hr ÷ q 12 hr IV
Forms: Tabs: 100, 250, 500, 750 mg
Oral suspension: 250, 500 mg/5 mL
Injection: 10 mg/mL

Generic Name: Clarithromycin
Trade Name: Biaxin, Biaxin XL (Mononaxy [France]; Clarusip [UK])
Drug Class: Macrolide
Use: Antibiotic
Cautions: Renal
Dosing: 15 mg/kg/24 hr PO ÷ q 12 hr
Forms: Film tabs: 250, 500 mg
Extended-release tabs: 500 mg
Granules for suspension: 125, 250 mg/5 mL

Generic Name: Clindamycin
Trade Name: Cleocin-T, Cleocin (Dalacine, Dalacine-T [France])
Drug Class: Semisynthetic antibiotic
Use: Antibiotic
Dosing: >7 days and >2 kg: 5 mg/kg/dose q 6 hr IM/IV
Children: 10-30 mg/kg/24 hr ÷ q 6-8 hr PO
25-40 mg/kg/24 hr ÷ q 6-8 hr IM/IV
Forms: Suspension: 75 mg/5 mL
Caps: 75, 150, 300 mg
Injection: 150 mg/mL

Generic Name: Co-trimoxazole, trimethoprim-sulfamethoxazole (TMP-SMX)
Trade Name: Bactrim, Septra, Sulfatrim (Bactekod, Bactrin [France]; Bactrim, Chemotrim, Comixco [UK])
Drug Class: Sulfonamide derivative
Use: Antibiotic
Cautions: Renal
Dosing: Based on TMP component
Children: 8-10 mg/kg/24 hr ÷ bid PO
Forms: Suspension: 40 mg TMP/200 mg SMX per 5 mL
Tabs: 80 mg TMP/400 mg SMX; 160 mg TMP/800 mg SMX
Injection: 16 mg TMP/mL; 80 mg SMX/mL

Generic Name: Codeine
Trade Name: (Neo-Codione, Paderyl, Pectoral [France]; Evacode, Galcodine [UK])
Drug Class: Narcotic
Use: Narcotic, analgesic, antitussive
Cautions: Renal
Dosing: Analgesic: 0.5-1 mg/kg/dose q 4-6 hr PO (not to exceed 60 mg/dose)
Forms: Tabs: 15, 30, 60 mg
Syrup: 60 mg/5 mL
Solution, oral: 15 mg/5 mL
Injection: 30, 60 mg

Generic Name: Desmopressin acetate
Trade Name: DDAVP (Minnin [France]; DDAVP, Desmospray [UK])
Drug Class: Vasopressin analogue
Use: Nocturnal enuresis
Dosing: 0.2-0.6 mg qhs PO
Intranasal: 10-40 μg qhs
Forms: Tabs: 0.1, 0.2 mg
Nasal spray: 10 μg/spray

Generic Name: Doxazosin mesylate
Trade Name: Cardura
Drug Class: Selective α-adrenergic inhibitor
Use: Voiding dysfunction
Dosing: <50 kg: Loading dose 0.5 mg qhs, then 0.5-1 mg qhs PO
Forms: 1, 2, 4, 8 mg

Generic Name: Doxycycline
Trade Name: Vibramycin, Periostat (Vibramycinex [France] Cyclodox, Vibramycin [UK])
Drug Class: Tetracycline derivative
Use: Antibiotic
Cautions: Sun exposure
Dosing: ≤45 kg: 5 mg/kg/24 hr ÷ bid PO/IV × 1 followed by 2.5-5 mg/kg/24 hr ÷ qd bid PO/IV
≥45 kg: 100 mg bid PO/IV × 1 followed by 100-200 mg/24 hr ÷ qd bid PO/IV
Forms: Caps: 20, 50, 100 mg
Tabs: 20, 50, 100 mg
Syrup: 50 mg/5 mL
Suspension: 25 mg/5 mL
Injection: 100, 200 mg

Generic Name: Flavoxate hydrochloride
Trade Name: Urispas
Drug Class: Urinary tract antispasmodic
Use: Voiding dysfunction
Dosing: 3 mg/kg q 8-12 hr PO
Forms: Tablets: 100 mg

Generic Name: Fluconazole
Trade Name: Diflucan (Triflucan [France]; Diflucan [UK])
Drug Class: Synthetic triazole antifungal
Use: Antifungal
Cautions: Renal
Dosing: Neonates: Loading dose 6-12 mg/kg/IV/PO, then >14 days 5 mg/kg qd
Children: Loading dose 10 mg/kg IV/PO, then 3-6 mg/kg/24 hr IV/PO
Forms: Oral suspension: 10, 40 mg/mL
Tabs: 50, 100, 150, 200 mg
Injection: 2 mg/mL

Generic Name: Furosemide
Trade Name: Furomide, Lasix (Furosemix, Lasilix [France]; Lasic, Froop [UK])
Drug Class: Loop diuretic
Use: Diuretic
Dosing: Neonates: 0.5-1 mg/kg/dose q 8-24 hr IV/PO
Children: 0.5-2 mg/kg/dose q 6-12 hr IV/PO
Forms: Tabs: 20, 40, 80 mg
Suspension: 10 mg/mL, 40 mg/5 mL
Injection: 10 mg/mL

Generic Name: Gentamicin
Trade Name: Garamycin (Gentabilles, Gentalline, Martigenta [France]; Cidomycin, Garamycin, Genticin [UK])
Drug Class: Aminoglycoside
Use: Antibiotic
Cautions: Renal
Dosing: Infants >7 days and >37 wk gestation: 2.5 mg/kg/24 hr ÷ q 8 hr IV/IM
Children: 6-7.5 mg/kg/24 hr ÷ q 8 hr IV/IM
(*Note*: Therapeutic peak levels 6-10 mg/L; therapeutic trough <2 mg/L)
Forms: Injection: 10, 40 mg/mL

Generic Name: Hydrochlorothiazide
Trade Name: Esidrix, Hydro-T, Hydrodiuril (Esidrix[France]; Esidrix [UK])
Drug Class: Thiazide
Use: Diuretic
Dosing: <6 mo: 2-4 mg/kg/24 hr ÷ q 12 hr PO
>6 mo: 2 mg/kg/24 hr ÷ q 12 hr PO
Forms: Tabs: 25, 50, 100 mg
Capsules: 12.5 mg

Generic Name: Hyoscyamine sulfate
Trade Name: Levsin
Drug Class: Anticholinergic/antispasmodic
Use: Bladder spasms
Dosing: <2 yr and 3.4 kg: 4 drops q 4 hr prn PO
5 kg: 5 drops q 4 hr prn PO
7 kg: 6 drops q 4 hr prn PO
10 kg: 8 drops q 4 hr prn PO
2-12 yr: ½-1 tablet slow release q 4 hr prn PO
2-12 yr and 10 kg: 1.25 mL elixir q 4 hr prn PO
20 kg: 2.50 mL elixir q 4 hr prn PO
40 kg: 3.75 mL elixir q 4 hr prn PO
50 kg: 5 mL elixir q 4 hr prn PO
Forms: Sublingual tabs: 0.125 mg
Extended-release tabs: 0.375 mg
Elixir: 0.125 mg/5 mL
Drops: 0.125 mg/mL

Generic Name: Ibuprofen
Trade Name: Motrin, Advil, Nuprin (Advil, Algifene, Analgyl [France]; Advil, Apsifen, Brufen [UK])
Drug Class: Nonsteroidal anti-inflammatory drug
Use: Analgesic/antipyretic
Cautions: Renal
Dosing: Children: 5-10 mg/kg/dose q 6-8 hr prn PO
Forms: Suspension: 100 mg/5 mL
Oral drops: 40 mg/mL
Chewable tabs: 50, 100 mg
Caplets: 100 mg
Tabs: 100, 200, 300, 400, 600, 800 mg

Generic Name: Imipramine
Trade Name: Tofranil, Janamine (Tofranil [France]; Tofranil [UK])
Drug Class: Tricyclic antidepressant
Use: Nocturnal enuresis
Dosing: >6 yr: initial 10-25 mg PO qhs
<12 yr: maximum 50 mg/24 hr
>12 yr: maximum 75 mg/24 hr
Forms: Tabs: 10, 25, 50 mg
Caps: 75, 100, 125, 150 mg

Generic Name: Ketorolac
Trade Name: Toradol (Tora-dol [France]; Acular, Toradol [UK])
Drug Class: Nonsteroidal anti-inflammatory drug
Use: Pain control
Cautions: Renal
Dosing: 0.5 mg/kg/dose q 6 hr, maximum dose 30 mg/q 6 hr IM/IV
10 mg/q 6 hr, maximum dose 40 mg/24 hr PO
Forms: Injection: 15, 30 mg/mL
Tabs: 10 mg

Generic Name: Lidocaine
Trade Name: Xylocaine (Mesocaine, Xylocaine [France]; Xylocaine, Rinsled [UK])
Drug Class: Local anesthetic
Use: Anesthetic
Dosing: Without epinephrine: 4.5 mg/kg/dose maximum dose
With epinephrine: 7 mg/kg/dose maximum dose
Forms: Injection: 0.5, 1, 1.5, 2, 4, 10, 20%, 1:50,000 epinephrine, 1:100,000 epinephrine, 1:200,000 epinephrine

Generic Name: Lidocaine/prilocaine
Trade Name: EMLA (eutectic mixture of lidocaine and prilocaine
Drug Class: Topical analgesic
Use: Pain control
Dosing: ≤5 kg: 1 g
≥5 kg: 2 g
≥10 kg: 10 g
≥20 kg: 20 g
Forms: Cream: Lidocaine 2.5% + prilocaine 2.5%

Generic Name: Loracarbef
Trade Name: Lorabid
Drug Class: Carbacephem
Use: Antibiotic
Cautions: Renal
Dosing: < 12 yr: 15 mg/kg/24 hr ÷ q 12 hr PO
>13 yr: 200 mg q 12 hr PO
Forms: Suspension: 100, 200 mg/5 mL
Caps: 200, 400 mg

Generic Name: Mannitol
Trade Name: Osmitrol, Resectisol (Doulax, Cyptocodine [France])
Drug Class: Osmotic diuretic
Use: Diuresis
Cautions: Renal
Dosing: 0.5-1 mg/kg/dose, maintenance 0.25-0.5 g/kg/dose q 4-6 hr IV
Forms: Injection: 50, 100, 150, 200, 250 mg/mL

Generic Name: Meperidine
Trade Name: Demerol
Drug Class: Narcotic
Use: Pain control
Dosing: 1-1.5 mg/kg/dose q 3-4 hr IV/IM/PO
Forms: Syrup: 50 mg/5 mL
Tabs: 50, 100 mg

Generic Name: Methicillin
Drug Class: Penicillin (penicillinase resistant)
Use: Antibiotic
Cautions: Renal
Dosing: Neonates: >7 days and >2 kg: 100-200 mg/kg/24 ÷ q 6 hr IM/IV
Neonates: >1 mo: 150-400 mg/kg/24 hr ÷ q 4-6 hr IM/IV
Forms: Injection: 1, 4, 6, 10 g

Generic Name: Methylene blue
Trade Name: Urolene Blue (Vitableu [France])
Use: Coloration of urine
Cautions: Renal
Dosing: 1-2 mg/kg/dose IV over 5 min, may repeat in 1 hr

Generic Name: Metoclopramide
Trade Name: Clopra, Maxolon, Reglan (Primperoxane [France] Gastroflux, Gastrese [UK])
Drug Class: Prokinetic agent
Use: Antiemetic
Cautions: Renal
Dosing: 0.1-0.2 mg/kg/dose qid IV/IM/PO, maximum dose 0.8 mg/kg/24 hr
Forms: Tabs: 5, 10 mg
Injection: 5 mg/mL
Syrup: 5 mg/5 mL
Solution: 10 mg/mL

Generic Name: Metronidazole
Trade Name: Flagyl
Drug Class: Antiprotozoal
Use: Antibiotic
Cautions: Renal
Dosing: *Clostridium difficile* infection: 30 mg/kg/24 hr ÷ q 6 hr IV/PO
Trichomoniasis: 15 mg/kg/24 hr ÷ q 8 hr PO
Forms: Suspension: 50, 100 mg/mL
Tabs: 250, 500 mg
Injection: 500 mg

Generic Name: Morphine sulfate
Trade Name: (Moscontin, Skenan [France]; Morcap, Oramorph, Sevredol [UK])
Drug Class: Narcotic
Use: Analgesia
Dosing: Neonates: 0.05-0.2 mg/kg/dose IM, slow IV q 4 hr
Infants and children: PO: 0.2-0.5 mg/kg/dose q 4-6 hr
Infants and children: IM/IV/SQ: 0.1-0.2 mg/kg/dose q 2-4 hr, maximum dose 15 mg/dose
Forms: Oral solution: 10, 20 mg/5 mL
Tabs: 15, 30 mg
Controlled-release tabs: 15, 30, 60, 100 mg
Rectal suppository: 5, 10, 20, 30 mg
Injection: 0.5, 1, 2, 3, 4, 5, 8, 10, 15, 25 mg/mL

Generic Name: Nafcillin
Trade Name: Unipen, Nafcil, Nallpen
Drug Class: Penicillin (penicillinase resistant)
Use: Antibiotic
Cautions: Renal
Dosing: Neonates: >7 days and >2 kg: 100 mg/kg/24 hr ÷ q 6 hr IM/IV
Infants and children: 50-100 mg/kg/24 hr ÷ q 6 hr PO/IM/IV
Forms: Tabs: 500 mg
Caps: 250 mg
Solution: 250 mg/5 mL
Injection: 0.5, 1, 2, 4, 10 g

Generic Name: Neomycin/polymyxin B/± bacitracin
Trade Name: Neosporin, Neosporin GU Irrigant (Atebemyxine, Bacteomycine [France]; Adcortyl/Granedoin, Audicort [UK])
Use: Topical antibiotic
Dosing: Apply tid
Forms: Solution, genitourinary irrigant: 40 mg neomycin, 200,000 U polymyxin B/mL

Generic Name: Nitrofurantoin
Trade Name: Furadantin, Macrodantin, Macrobid (Furadantine, Furadoine, Microdoine [France]; Furadantin, Macrobid, Macrodantin [UK])
Use: Antibiotic
Cautions: Renal
Dosing: >1 mo: 5-7 mg/kg/24 hr ÷ q 6 hr PO
Prophylaxis: 1-2 mg/kg/dose qhs PO
Forms: Suspension: 25 mg/5 mL
Caps: 25, 50, 100 mg

Generic Name: Ondansetron
Trade Name: Zofran (Zophren [France]; Zofran [UK])
Drug Class: 5-HT3 antagonist
Use: Antiemetic
Dosing: >3 yr: 0.15 mg/kg/dose q 4 hr IV
Forms: Solution: 4 mg/5 mL
Tabs: 4, 8 mg

Generic Name: Oxycodone and acetaminophen
Trade Name: Tylox, Percocet, Roxilox
Drug Class: Analgesic and narcotic
Use: Analgesia
Dosing: 0.05-0.15 mg/kg/dose q 4-6 hr PO (maximum 10 mg/dose) based on oxybutynin
Forms: Solution: 325 mg acetaminophen, 5 mg oxycodone per 5 mL
Tabs: 325 mg acetaminophen, 5 mg oxycodone

Generic Name: Phenazopyridine HCl
Trade Name: Pyridium (Pyndium [France])
Drug Class: Urinary analgesic
Use: Dysuria
Cautions: Renal
Dosing: Children 6-12 yr: 12 mg/kg/24 hr ÷ tid PO
Forms: Suspension: 10 mg/mL
Tabs: 95, 100, 200 mg

Generic Name: Piperacillin
Trade Name: Pipracil (Piperilline [France]; Piperil [UK])
Drug Class: Penicillin
Use: Antibiotic
Cautions: Renal
Dosing: Neonates >7 days and >36 wk gestation: 300 mg/kg/24 hr ÷ q 6 hr IM/IV
Infants and children: 200-300 mg/kg/24 hr IM/IV ÷ q 4-6 hr
Forms: Injection: 2, 3, 4, 40 g

Generic Name: Piperacillin/tazobactam
Trade Name: Zosyn (Tazocilline [France]; Tazocin [UK])
Drug Class: Penicillin (β-lactamase inhibitor)
Use: Antibiotic
Cautions: Renal
Dosing: <6 mo: 150-300 mg/kg/24 hr ÷ q 6-8 hr IV
>6 mo: 300-400 mg/kg/24 hr ÷ q 6-8 hr IV
Forms: Injection: 8:1 ratio piperacillin to tazobactam

Generic Name: Polyethylene glycol–electrolyte solution
Trade Name: GoLYTELY, Co-Lav, Colovage, CoLyte, GoEvac (Colo Peg, Fortrans [France]; Movicol, Kleanprep & Golytely, Colyte [UK])
Use: Colonic lavage solution
Dosing: Children: 25-40 mg/kg/hr PO
Forms: Powder for oral suspension

Generic Name: Prazosin
Trade Name: Minipress
Drug Class: α_1-Adrenergic blocking agent
Use: Voiding dysfunction
Dosing: 5 μg/kg test, 25-150 μg/kg/24 hr q 6 hr PO
Forms: Caps: 1, 2, 5 mg

Generic Name: Prochlorperazine
Trade Name: Compazine
Use: Antiemetic
Dosing: 0.4 mg/kg/24 hr ÷ q 6-8 hr PO/PR
0.1-0.15 mg/kg/dose tid IM
Forms: Syrup: 5 mg/5 mL
Suppository: 2.5, 5, 25 mg
Tabs: 5, 10, 25 mg

Generic Name: Propantheline
Trade Name: Pro-Banthine
Use: Anticholinergic
Dosing: 0.5 mg/kg q 6-12 hr PO
Forms: Tabs: 7.5, 15 mg

Generic Name: Pseudoephedrine
Trade Name: Sudafed
Drug Class: Sympathomimetic
Use: Voiding dysfunction
Dosing: 4 mg/kg/24 hr ÷ q 6 hr PO
Forms: Liquids: 15, 30 mg/5 mL
Tabs: 30, 60 mg

Generic Name: Ranitidine HCl
Trade Name: Zantac (Azantac, Raniplex [France]; Zantac, Rantec, Ranaps [UK])
Drug Class: Histamine$_2$ antagonist
Use: Hematuria/dysuria syndrome secondary to gastric augmentation
Cautions: Renal
Dosing: Children: 4-5 mg/kg/24 hr ÷ q 8-12 hr PO, maximum dose 6 mg/kg/24 hr
Forms: Syrup: 15 mg/mL
Tabs: 75, 150, 300 mg

Generic Name: Sulfisoxazole
Trade Name: Gantrisin
Drug Class: Sulfonamide derivative
Use: Antibiotic
Cautions: Renal
Dosing: Prophylaxis: 50 mg/kg dose qhs PO
Forms: Suspension: 500 mg/5 mL
Syrup: 500 mg/5 mL
Tabs: 500 mg

Generic Name: Terazosin
Trade Name: Hytrin
Drug Class: α_1-Adrenergic agonist
Use: Voiding dysfunction
Dosing: 0.5-10 mg qhs PO
Forms: 1, 2, 5, 10 mg

Generic Name: Tobramycin
Trade Name: Nebcin, Tobrex (Nebcine, Tobrex [France]; Nebcin, Tobralex [UK])
Drug Class: Aminoglycoside
Use: Antibiotic
Cautions: Renal
Dosing: 6-7.5 mg/kg/24 hr ÷ q 8 hr IV/IM
Therapeutic Levels: Peak: 6-10 mg/L
Trough: <2 mg/L
Forms: Injection: 10, 40 mg/mL

Generic Name: Tolterodine
Trade Name: Detrol
Drug Class: Anticholinergic
Use: Voiding dysfunction
Dosing: 0.5-2 mg q 12 hr PO
Forms: Tablets: 1, 2 mg

Generic Name: Vancomycin
Trade Name: Vancocin (Vancocine [France]; Vancocin [UK])
Drug Class: Tricyclic glycopeptide
Use: Antibiotic
Cautions: Renal
Dosing: 40 mg/kg/24 hr ÷ q 6-8 hr
Forms: Capsules: 125, 250 mg
Injection: 500, 1000 mg; 2, 5, 10 g